PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]CAMCEVI®

leuprolide injectable emulsion

Extended Release Emulsion, 42 mg leuprolide (as leuprolide mesylate), Subcutaneous Injection (6-Month)

Gonadotropin Releasing Hormone Analogue

Accord Healthcare Inc.
3535 boul. St. Charles suite 704
Kirkland, QC, H9H 5B9
Canada

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CAMCEVI (leuprolide mesylate) is indicated for:

- treatment of adult patients with advanced prostate cancer.

1.1 Pediatrics (< 18 years of age)

- No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics (> 65 years of age)

- The mean age of the male patients studied in the clinical trials was 71 years (range 51–88 years). The safety and efficacy of CAMCEVI was established in this population (see 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

CAMCEVI is contraindicated in:

- patients with hypersensitivity to gonadotropin releasing hormone (GnRH) analogues, or any of the components of CAMCEVI. Anaphylactic reactions including anaphylactic shock to synthetic GnRH or GnRH analogues have been reported in post-marketing surveillance. For a complete listing, see the section 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- women and paediatric patients.
- women who are or may become pregnant.
- women who are nursing.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

CAMCEVI (leuprolide mesylate) should be prescribed by a qualified physician experienced in the use of hormonal therapy in prostate cancer.

The following are clinically significant adverse events:

- Clinical testosterone flare reaction in men with prostate cancer (see **7 WARNINGS AND PRECAUTIONS,** General)
- Pituitary apoplexy (see **7 WARNINGS AND PRECAUTIONS,** Endocrine and Metabolism)
- Osteoporosis (see **7 WARNINGS AND PRECAUTIONS**, Endocrine and Metabolism).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- CAMCEVI should be administered by a healthcare professional.

- CAMCEVI, 42 mg administered subcutaneously is designed to provide continuous extended release of leuprolide for 6 months.

4.2 Recommended Dose and Dosage Adjustment

- CAMCEVI 42 mg (6-Month)
  The recommended dose of CAMCEVI is 42 mg administered every six months as a single subcutaneous injection (see 4.4 ADMINISTRATION).

4.4 Administration

CAMCEVI is administered by subcutaneous injection, whereupon it forms a solid drug delivery depot releasing leuprolide mesylate over 6 months. The injectable emulsion contains approximately 42 mg of leuprolide base (equivalent to approximately 48 mg leuprolide mesylate). The recommended dosing is 1 subcutaneous injection every 24 weeks.

As with other drugs administered by subcutaneous injection, the injection site should vary periodically. The specific injection location chosen should be an area with sufficient soft or loose subcutaneous tissue. In clinical trials, the injection was administered in the upper- or mid-abdominal area. Areas with brawny or fibrous subcutaneous tissue or locations that can be rubbed or compressed (i.e., with a belt or clothing waistband) should be avoided.

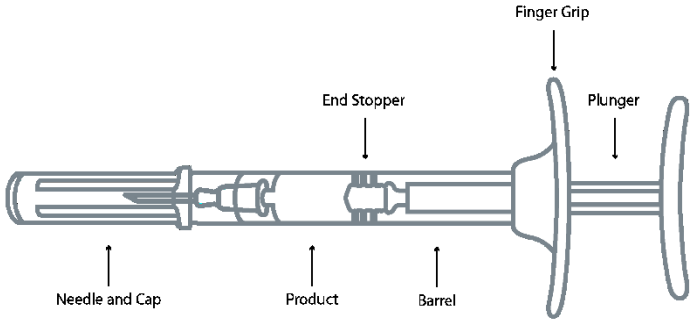
Administration Procedure

IMPORTANT: Allow the product to reach room temperature before using. The use of gloves is recommended during administration [Occupational Health and Safety (OH&S)].

Follow the instructions as directed to ensure proper preparation of CAMCEVI prior to administration:

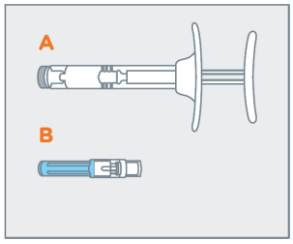
CAMCEVI 42 mg kit contains:

- One blister with:
  - One sterile pre-filled plastic syringe closed with elastomeric grey tip cap, plunger and finger grip
  - One sterile 18 gauge, 5/8 inch needle
- One Point-Lok® needle protection device (non-sterile)

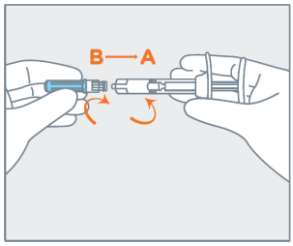


Syringe Assembly

Remove contents



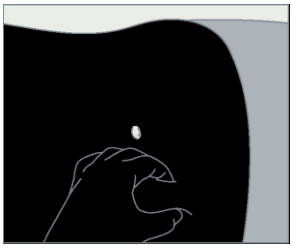
Assemble the Needle



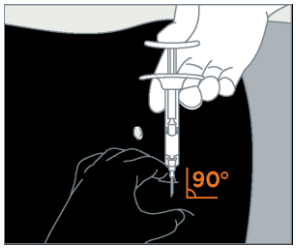
1. Keep contents in their original, sealed blister container and allow pre-filled syringe to sit at room temperature for 30 minutes prior to subcutaneous injection.
2. On a clean, dry surface, remove pre-filled CAMCEVI 42 mg syringe (A) and needle cartridge (B) from the blister container. Visually inspect the contents prior to use.
3. Remove the gray cap from the syringe (A).
4. Twist the clear cap off the bottom of the needle cartridge (B).
5. Attach the needle (B) to the end of the syringe (A) by pushing and turning until firmly connected. Do not over twist the needle and strip the threading.

Administration Procedure

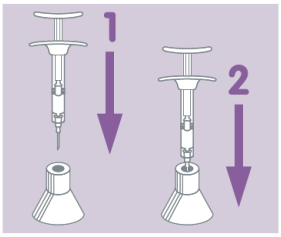
Prepare the Injection Site



Administer Treatment



Insert and Discard Needle



1. Choose an injection site on the upper- or mid-abdominal area that has not recently been used. Clean the injection site with an alcohol swab. Do **NOT** inject in areas with brawny or

fibrous subcutaneous tissue or locations that can be rubbed or compressed (i.e., with a belt or clothing waistband).
2. Pull the blue cover off the needle (B). Grab and bunch the skin around the injection site with one hand. Insert the needle at a 90° angle, then release the bunched skin.
3. Inject the full contents of the syringe with a slow and steady push, then withdraw the needle at the same 90° angle used for insertion.
4. Do not remove the needle from the syringe. Use the enclosed Point-Lok® device to prevent needle sticks. Place the Point-Lok® needle protection device, supplied within the CAMCEVI 42 mg kit, on a secured flat surface.
5. Immediately after use of the needle, gently insert the exposed needle into the Point-Lok® device opening at top of the device.
6. Push needle into the top opening until it is firmly inserted into the Point-Lok® device. This action will seal the needle tip and lock the needle firmly into the device.
7. After use, place the used syringe with needle protected in a suitable sharps container. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

4.5 Missed Dose

Maintaining testosterone suppression is important in treating the symptoms of hormone-dependent prostate cancer. Missing an appointment by a few days should not disrupt the benefits of treatment, but keeping a consistent schedule of leuprolide injections is an important part of treatment. Call your doctor for instructions if you miss a dose.

5 OVERDOSAGE

There is no clinical experience with the effects of an acute overdose. There is no known antidote for CAMCEVI overdose. In the event of an overdose, stop CAMCEVI, undertake general supportive measures until clinical toxicity has been diminished or resolved.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Extended-release emulsion for injection/42 mg leuprolide (equivalent to approximately 48 mg leuprolide mesylate) in Schott syringe	N-methylpyrrolidone Poly(D,L-Lactide)

CAMCEVI is available as follows:

Kit Contents
CAMCEVI 42 mg pre-filled syringe, a sterile 18 gauge needle, and a non-sterile needle protection device.

- CAMCEVI is a sterile, off-white to pale yellow, viscous and opalescent injectable emulsion.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

CAMCEVI, like other GnRH analogues, causes a transient increase in serum concentration of testosterone during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction. Cases of spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with GnRH analogues. If spinal cord compression or renal impairment due to ureteral obstruction develops, standard treatment of these complications should be instituted.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should begin leuprolide therapy under close supervision.

Administration procedure should be followed, as lack of clinical efficacy may occur due to incorrect administration of the product (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 4.4 Administration, Administration Procedure).

Carcinogenesis and Mutagenesis

No carcinogenicity studies or genotoxicity studies have been conducted specifically with CAMCEVI.

Two-year carcinogenicity studies conducted with leuprolide in rats found increased incidences of pituitary hyperplasia and adenomas, pancreatic islet-cell adenomas, and testicular interstitial cell adenomas (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity).

Genotoxicity studies performed with leuprolide using bacterial and mammalian systems found no evidence of genotoxic potential (see 16 NON-CLINICAL TOXICOLOGY, Genotoxicity).

Cardiovascular

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH analogues in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors. Reports of events related to cardiovascular ischemia including myocardial infarction, stroke and cardiovascular-related deaths have been reported in patients treated with GnRH analogues.

Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential cardiovascular risk.

Patients receiving GnRH analogues should be monitored for symptoms and signs suggestive of development of cardiovascular disease, and management according to current clinical practice and guidelines should be considered (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Effect on QT/QTc interval

Androgen deprivation therapy may prolong the QT/QTc interval. In patients with a history of or risk factors for QT prolongation including congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure, and/or in patients receiving concomitant medicinal products that might prolong the QT interval, physicians should assess whether the benefits of androgen deprivation therapy outweigh the potential risks including the potential for Torsade de pointes prior to initiating CAMCEVI.

Driving and Operating Machinery

Fatigue and dizziness have been reported in patients taking CAMCEVI.

Therefore, exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Pituitary apoplexy

During post-marketing surveillance, serious cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of GnRH analogues, with a majority occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention is required. Pre-existing gonadotropin-secreting pituitary adenoma was diagnosed in a majority of patients. If the presence of macroadenomas is evidenced by imaging and biochemical assessments, this should be surgically removed prior to start of GnRH analogues including CAMCEVI treatment.

Hypogonadism

Long-term administration of leuprolide will cause suppression of pituitary gonadotropins and gonadal hormone production with clinical symptoms of hypogonadism. These changes have been observed to reverse on discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

Hyperglycemia and Diabetes

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogues. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or glycosylated haemoglobin (HbA1c) periodically in patients receiving a GnRH analogue and manage with current practice for treatment of hyperglycaemia or diabetes.

Hematologic

Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered.

Monitoring and Laboratory Tests

Patients with vertebral and/or brain metastases as well as patients with urinary tract obstruction should be closely monitored during the first few weeks of therapy.

Monitor response to leuprolide by periodically measuring serum concentrations of testosterone and prostate specific antigen. Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

Testosterone levels should also be evaluated in the case of suspected or known handling errors, as lack of efficacy may result from incorrect preparation or administration. Baseline risk factors of cardiovascular diseases should be assessed. Patients receiving leuprolide should be monitored periodically for risk factors, signs and symptoms of cardiovascular diseases. In addition, baseline ECG recording and serum potassium, calcium, and magnesium levels are recommended. Monitoring of ECG and serum electrolyte levels during treatment should also be considered for those at risk for electrolyte abnormality and QTc prolongation.

Blood glucose levels and/or glycosylated hemoglobin (HbA1c) should be checked periodically in patients treated with GnRH analogues and more frequently in diabetic patients (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

The effects of leuprolide on bone lesions may be monitored by bone scans, while its effects on prostatic lesions may be monitored by ultrasonography, and/or CT scan in addition to digital

rectal examination. Intravenous pyelogram, ultrasonography, or CT scan may also be utilized to diagnose or assess the status of obstructive uropathy.

Musculoskeletal

Decreased bone mineral density can be anticipated with long term use of a GnRH analogue. Androgen deprivation therapy is associated with increased risks of osteoporosis and skeletal bone fractures. The risk of skeletal bone fracture increases with the duration of androgen deprivation therapy. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

In patients with significant risk factors for decreased bone mineral content and/or bone mass such as chronic alcohol and/or tobacco use, presumed or strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, CAMCEVI may pose an additional risk. In these patients, risk versus benefit must be weighed carefully before therapy with CAMCEVI is initiated.

Neurologic

Convulsions have been reported in patients on leuprolide with or without a history of predisposing factors in the post-market setting. Convulsions are to be managed according to the current clinical practice.

Tumor Flare

CAMCEVI, like other GnRH analogues, causes a transient increase in serum levels of testosterone during the first week of treatment, declining thereafter to baseline levels or below by the end of the second week of treatment. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer, may occasionally develop during the first few weeks of CAMCEVI treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically.

As with other GnRH analogues, isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.

Reproductive Health: Female and Male Potential

- **Fertility**

Based on findings in animals and mechanism of action, CAMCEVI may impair fertility in males of

reproductive potential (see 10 CLINICAL PHARMACOLOGY, 16 NON-CLINICAL TOXICOLOGY).

Continuous daily administration of leuprolide results in decreased levels of luteinizing hormone (LH), follicle stimulating hormone (FSH) and reduction of testosterone to castrate levels.

- **Teratogenic Risk**

CAMCEVI is contraindicated in women who are or may become pregnant (see 2 CONTRAINDICATIONS). Based on findings in animals, CAMCEVI may cause fetal harm if administered to pregnant women (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Respiratory

There have been post-marketing reports of interstitial pneumonitis associated with leuprolide use. Treatment should be discontinued immediately if the patient develops any signs or symptoms suggestive of interstitial lung disease.

7.1 Special Populations

7.1.1 Pregnant Women

Leuprolide is contraindicated in women who are or may become pregnant (see 2 CONTRAINDICATIONS). Studies in animals have shown leuprolide can result in embryotoxicity and lethality (see 16 NON-CLINICAL TOXICOLOGY). CAMCEVI is not indicated for use in women as safety and efficacy have not been established in this group of patients.

7.1.2 Breast-feeding

CAMCEVI is contraindicated for use in nursing women as safety and efficacy have not been established in this group of patients.

7.1.3 Pediatrics (< 18 years of age)

CAMCEVI is contraindicated for use in children as safety and efficacy have not been established in this group of patients.

7.1.4 Geriatrics (> 65 years of age)

The mean age of the male patients studied in the clinical trials was 71 years (range 51–88 years). The safety and efficacy of CAMCEVI was established in this population. (See 14 CLINICAL TRIALS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of CAMCEVI was evaluated in a clinical trial involving patients with advanced prostate cancer who received at least one dose of CAMCEVI. CAMCEVI, like other GnRH analogues, caused a transient increase in serum testosterone concentrations during the first week of treatment, declining thereafter to baseline levels or below by the end of the second week of treatment. Therefore, potential exacerbations in signs and symptoms of the disease during the first weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems (such as weakness and/or paresthesia of the lower limbs) or increase the obstruction (see 7 WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

In an open-label, non-comparative clinical trial (FP01C13-001), patients with advanced prostate cancer received CAMCEVI administered subcutaneously at a dose of 42 mg on Day 0 and Day 168. Of 137 patients enrolled, 93% received both doses of CAMCEVI. The median follow-up duration was 336 days.

The most common adverse reactions (incidence ≥ 10%) were hot flush, hypertension, injection site reactions, upper respiratory infections, musculoskeletal pain, fatigue, and pain in extremity.

Serious Adverse Events (SAE) occurred in 15% of patients treated with CAMCEVI. The most common (≥1%) SAE observed was subdural haematoma (1.5%).

Fatal adverse reactions occurred in 2% of patients including one due to cerebrovascular accident (0.7%), one due to pulmonary embolism (0.7%), and one due to metastatic prostate cancer to lungs (0.7%) and acute kidney injury.

Discontinuation occurred in 11% of subjects. The most common reason for discontinuation was due to adverse events in 4% of patients including acute kidney injury, atrial fibrillation, cerebrovascular accident, death, hormone refractory prostate cancer and metastatic prostate cancer.

The following adverse events (all grades) occurred in the clinical trial of CAMCEVI and were reported in ≥5% of patients (Table 2).

Table 2 Summary of Adverse Events Reported in ≥ 5% of Patients Treated with CAMCEVI

Adverse Reaction	N = 137	
	All Grades (%)	Grade 3-4 (%)
Vascular disorders		
Hot flush[a]	50	0
Hypertension[b]	15	0
General disorders and administration site conditions		
Injection site reactions[c]	11	0
Fatigue[d]	10	0
Infections and infestations		
Upper respiratory tract infection[e]	11	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[f]	11	0
Pain in extremity	10	0
Arthralgia	7	0
Renal and urinary disorders		
Micturition urgency[g]	6	0
Nocturia	6	0
Nervous system disorders		
Dizziness[h]	5	0.7

[a] includes hot flush and flushing

[b] includes hypertension, essential hypertension, and blood pressure increased

[c] includes injection site pain, injection site erythema, injection site hemorrhage, injection site nodule, injection site paraesthesia, injection site pruritus, and injection site warmth

[d] includes fatigue and asthenia

[e] includes upper respiratory tract infection, sinusitis, and nasopharyngitis

[f] includes musculoskeletal pain, back pain, and bone pain

[g] includes micturition urgency and dysuria

[h] includes dizziness, dizziness postural, vertigo, and vertigo positional.

8.3 Less Common Clinical Trial Adverse Reactions

The following are selected clinically significant adverse reactions reported in less than 5% of patients receiving CAMCEVI in study FP01C-13-001:

Cardiac disorders: Atrial fibrillation, myocardial infarction

Cardiovascular: Deep vein thrombosis

Eye disorders: Vision blurred

Infections and infestations: Urinary tract infection

Injury, poisoning and procedural complications:	Hip fracture
Investigations:	Alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, weight increased
Metabolism and nutrition disorders:	Obesity, decreased appetite, diabetes mellitus
Nervous system disorders:	Lethargy, amnesia, headache
Psychiatric:	Affect lability, confusional state, depression, irritability, loss of libido
Reproductive system and breast disorders:	Gynaecomastia
Skin:	Cold sweat, erythema, pruritus

The safety profile of CAMCEVI was further examined and followed in the open-label, single-arm safety extension study (FP01C-13-001-EX) with 30 subjects enrolled. No new safety signals were identified in the safety extension study.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Laboratory abnormalities were observed, but it was difficult to assess relationship to the drug treatment as most occurred in <3% of patients and most in 1 subject each. The following laboratory abnormalities occurred in the clinical trial for CAMCEVI and were reported in > 1% of patients (

Table 3).

Table 3 Summary of Laboratory Abnormalities

Lowest Level Term	Total (No=137) Grade 1–2 (%)	Total (No=137) Grade 3-4 (%)
Alanine aminotransferase increased	2.9%	0%
Aspartate aminotransferase increased	2.9%	0 0%
Alkaline phosphatase increased	1.5%	0 0%
White blood cells urine	1.5%	0%

Table 3 Summary of Laboratory Abnormalities

Lowest Level Term	Total (No=137) Grade 1–2 (%)	Total (No=137) Grade 3-4 (%)
increased		
Prostatic specific Antigen increased	1.5%*	0.7%

Note: *Two patients had clinically significant PSA increase in CAMCEVI trial, but only one of them had the increased PSA judged with severe clinical significance.

The following grade 1–2 laboratory abnormalities occurred in 1 subject each (0.7%): blood creatinine increased, blood lactic acid increased, decreased hemoglobin, eosinophil count increased, erythrocytes decreased, fasting blood glucose increased, gastric acid increased, hematocrit decreased, lymphocyte percentage decreased, neutrophil count increased/neutrophil percentage increased (1 subject each), potassium increased, urine red blood cells increased, and white blood cell increased.

8.5 Post-Market Adverse Reactions

During post-marketing surveillance of other leuprolide dosage forms and other patient populations, the following adverse events were reported.

Cardiovascular System: Hypotension;

Endocrine System: Pituitary apoplexy;

Eye disorders: Photosensitivity reactions;

Gastrointestinal System: Hepatic dysfunction;

General disorders and administration site conditions: Localized reactions including induration and abscess, fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath);

Hemic and Lymphatic System: Decreased white blood cells;

Integumentary System: Hair growth;

Central/Peripheral Nervous System: Convulsion, spinal fracture/paralysis, hearing disorder;

Miscellaneous: Hard nodule in throat, weight gain, increased uric acid;

Musculoskeletal System: Tenosynovitis-like symptoms, decreased bone density;

Respiratory System: Respiratory disorders; interstitial lung disease, anaphylactoid or asthmatic process

Skin and subcutaneous tissue disorders: Rash, urticarial.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with leuprolide.

No data is available on the interaction with alcohol.

9.4 Drug-Drug Interactions

No pharmacokinetic drug interactions were conducted with CAMCEVI.

Interactions with drugs have not been established.

Since androgen deprivation treatment may prolong the QTc interval, the concomitant use of leuprolide with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes should be carefully evaluated. Such medicinal products include but are not limited to the examples that follow: Class IA (e.g. quinidine, disopyramide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide, dronedarone), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine), antidepressants (e.g. amitriptyline, nortriptyline), opioids (e.g. methadone), macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g. moxifloxacin), antimalarials (e.g. quinine), azole antifungals, 5-hydroxytryptamine (5-HT3) receptor antagonists (e.g. ondansetron), and beta-2 adrenoceptor agonists (e.g. salbutamol).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Therapy with leuprolide results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after

leuprolide therapy may be affected.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Leuprolide, a GnRH analogue, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation of gonadotropins, chronic administration of leuprolide results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy.

In humans, subcutaneous administration of single daily doses of leuprolide result in an initial increase in circulating levels of LH and FSH, leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, long term administration of leuprolide results in decreased levels of LH and FSH. In males, testosterone is reduced to levels associated with castration (≤50ng/dL in serum). In pre-menopausal females, estrogens are reduced to post-menopausal levels.

10.2 Pharmacodynamics

Following the first dose of CAMCEVI, mean serum testosterone concentrations transiently increased, then fell to below castrate threshold levels (≤ 50 ng/dL) within 3 weeks and remained below castrate levels with continued treatment.

A post hoc analysis of ECG and serum concentration was performed because some subjects had high QTcF and dQTcF values during the study period. This analysis showed an increase in QTcF related to leuprolide treatment. The maximum observed dQTcF during treatment (12.4 msec [90% CI 8.44, 16.40 msec]) occurred on Day 168. Similar increases were noted on Days 28 and 336. Central tendency analysis and concentration-effect modeling indicate that the increase in QTcF was not related to leuprolide levels, but instead correlated with the reduced testosterone serum concentration induced by leuprolide. The mean increase in dQTcF exceeded 10 msec at the four ECG sampling time points from Day 28 through Day 336, and the upper boundary of the confidence interval in the concentration-effect model exceeded 10 msec at testosterone levels below 35 ng/dl.

Overall, nine subjects had outlier QTcF responses: QTcF ≥ 500 msec, or QTcF ≥ 480 msec with dQTcF ≥ 60 msec, or both.

The post hoc analysis did not detect a clinically relevant effect of leuprolide on heart rate, PR interval, or QRS interval.

10.3 Pharmacokinetics

Table 4 PK Parameters of Camcevi 42 mg in PK population

	First Dose			Second Dose		
PK Parameter	N	Mean	SD	N	Mean	SD
C_{max}, ng/mL	31	94.5	53.7	29	99.0	73.0
T_{max}, h	31	3.23 (1.17, 7.90)		29	2.08 (1.17, 8.00)	
$AUC_{0\text{-}6mon}$, day·ng/mL	29[a]	224	87.3	29	268	88.1
Vd (L)	31	13200	7333	29	11800	9412
$t_{1/2}$ (h)	31	939	430.2	29	1250	1577
CL (L/h)	31	13.8	20.90	29	7.39	2.433

[a] not reportable for 2 subjects

Absorption

The pharmacokinetics were observed during injections of CAMCEVI administered initially (n = 31 patients) and at 24 weeks (n = 29 patients). Following the first and the second doses of CAMCEVI, mean serum leuprolide concentrations rose rapidly to reach the C_{max} of 94.5 and 99.0 ng/mL at 3.23 and 2.08 hours (median T_{max}), respectively. Following the initial rapid increase, leuprolide concentrations declined gradually over the remaining duration of the dosing interval (Day 3 to Day 168). The mean serum concentrations during this "plateau" phase were mostly maintained at 0.497–2.57 (after Day 3 to Day 168) and 0.507–2.39 ng/ml (after Day 171 to Day 336) post the first and the second dose, respectively.

Distribution

The mean steady state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.

Metabolism

Leuprolide is a peptide that is primarily metabolized by peptidases and not by CYP enzymes.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M I concentrations were approximately 20% of mean leuprolide concentrations.

Elimination

In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half life of approximately 3 hours based on a 2-compartment model.

No drug excretion study was conducted specifically with CAMCEVI.

Special Populations and Conditions
The pharmacokinetics of the drug have not been determined in patients with hepatic or renal impairment.

- **Pediatrics:** CAMCEVI is contraindicated in pediatric patients (see 2 CONTRAINDICATIONS).
- **Geriatrics:** The mean age of the male patients studied in the clinical trials was 71 years (range 51–88 years). The safety and efficacy of CAMCEVI was established in this population. (See 14 CLINICAL TRIALS).
  - **Sex:** Only male patients were included in studies with CAMCEVI.
  - No clinically meaningful differences in systemic exposure of leuprolide were observed based on age, race, or body weight.

11 STORAGE, STABILITY AND DISPOSAL

Store CAMCEVI at a refrigerated temperature of 2°C to 8°C (35.6 ºF and 46.4 ºF). Protect CAMCEVI from light by storing in the original package until time of use. Do not freeze or shake.

12 SPECIAL HANDLING INSTRUCTIONS

CAMCEVI should be handled following Occupational Health and Safety (OH&S) safety guidelines. The use of gloves is recommended.

Keep contents in their original, sealed blister container and allow pre-filled syringe to sit at room temperature for 30 minutes prior to subcutaneous injection.

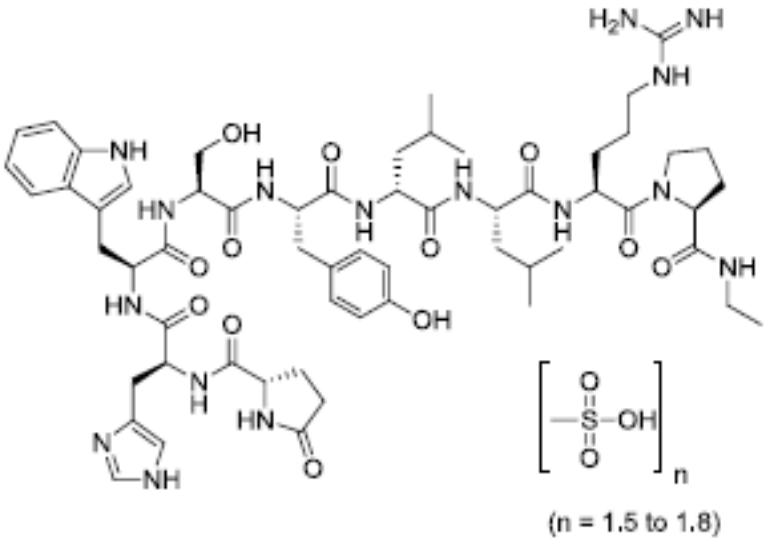
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Leuprolide mesylate
Chemical name:	5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide mesylate
Molecular formula and molecular mass:	$C_{59}H_{84}N_{16}O_{12} \cdot (CH_4O_3S)n$, n = 1.5–1.8 ; 1209.41 Daltons (free base)

Structural formula:



Physicochemical properties:	Leuprolide mesylate is a white to off-white powder, freely soluble in water, dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP); insoluble in acetone and acetonitrile; and the pKa is 6.1.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Indication 1: Treatment of Adult Patients with Advanced Prostate Cancer

Table 5 Summary of patient demographics for clinical trials in prostate cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range; in years)	Sex
FP01C-13-001	Open-label, single arm, phase 3, multi-centre, multi-national	CAMCEVI 42 mg is an injectable extended release emulsion containing 42 mg leuprolide (equivalent to approximately 48 mg as leuprolide mesylate), administered subcutaneously every 6 months	137	71.1 (51 to 88)	Male

The efficacy of CAMCEVI was evaluated in an open-label, single arm, multi-center, multinational phase 3 study in adult patients with histologically confirmed advanced prostate carcinoma (baseline morning serum testosterone level 150 ng/dL; Eastern Cooperative Oncology Group [ECOG] ≤ 2). A total of 137 subjects were enrolled and received at least one dose of the study drug (intent-to-treat [ITT] population), and 124 subjects completed the study without major protocol violations affecting the primary efficacy endpoint (per-protocol [PP] population). Of 137 subjects enrolled, 128 subjects received both doses of CAMCEVI (compliance of 93.4%).

The median age of the patients in the study was 71 years and all were male. The population was 90% white, 6% black, 4% Asian and 0.7% unknown. The mean and median duration with diagnosed prostate cancer was 4.9 and 2.0 years, respectively. With regard to disease stage, 23.4% (32/137) subjects had prostate carcinoma stage IV, 27.0% (37/137) subjects had prostate carcinoma stage III, 22.6% (31/137) subject had prostate carcinoma stage II, 2.9% (4/137) subjects had prostate carcinoma stage I, and 23.4% (32/137) subjects had unknown prostate carcinoma stage at baseline. There were 83.2% (114/137) subjects with Grade 0, 16.1% (22/137) subjects with Grade 1, and 0.7% (1/137) subject with Grade 2 in ECOG performance status at baseline. The median testosterone concentration at baseline was 440 ng/dL.

The primary endpoints of the study was to determine the percentage of subjects achieving serum testosterone suppression (<50 ng/dL) by week 4 (day 28), and maintaining that suppression from week 4 through week 48 (day 336) of treatment. To demonstrate clinical efficacy, the lower bound of the 95% confidence interval for the primary endpoint estimate was prespecified to be greater than 90%. Insufficient suppression of testosterone was defined as

suppression that did not occur by Day 28 or the occurrence of a testosterone level > 50 ng/dL between Day 28 and Day 336. The secondary endpoints consisted of post suppression excursions, percentage of patients that achieved and maintained testosterone suppression below 20ng/dL and serum PSA levels.

Study Results

In the ITT population serum testosterone levels were suppressed to castrate levels (≤ 50 ng/dL) by Day 28 following the first injection of CAMCEVI in 98.5% of the patients (135/137). The percentage of patients with testosterone suppression (≤ 50 ng/dL) from week 4 through week 48 was 97.0% in the ITT population (Table 6). The percentage of patients with testosterone suppression (≤ 20 ng/dL) was 69.3% (95/137) on Day 28, and 85.4% (117/137) on Day 336 in the ITT population. In the PP population, the percentage of patients with testosterone suppression (≤ 20 ng/dL) was 69.4% (86/124) on Day 28, and 92.7% (115/124) on Day 336.

Table 6 Primary Endpoint Results for Study FP01C-13-001

Population	# Enrolled/ completed	Percentage of subjects with serum testosterone ≤ 50 ng/dL (95% CI)	
		By Day 28	Day 28–Day 336
ITT[a]	137/137	98.5 (94.8–99.8)	97.0 (92.2–98.9)
PP[b]	137/124	99.2 (95.6–100.0)	97.6 (92.7–99.2)

[a] Any subject who received at least 1 dose of CAMCEVI

[b] Any subject who received 2 doses of CAMCEVI, followed the inclusion/exclusion criteria of the protocol, and had no major protocol violation

CI = confidence interval; ITT = intent-to-treat; PP = per protocol

Source: Main Study FP01C-13-001, Table 11-9 and Table 11-10

Two of 137 subjects (1.5%) did not reach castrate levels on Day 28. One subject had a baseline level of 498 ng/dL, and his testosterone level was suppressed to 61.4 ng/dL on Day 28, and then reached castrate levels at the next measurement (Day 56) of 9.2 ng/dL. This subject stayed below 50 ng/dL for the duration of the study. The second subject had a baseline value of 297 ng/dL, and his testosterone level was suppressed to 53.4 ng/dL on Day 28 and 59.8 ng/dL on Day 56 before rebounding to 257 ng/dL on Day 84 with accompanying increasing Prostate Specific Antigen (PSA) levels, at which time he was discontinued due to lack of efficacy. Following the second injection of CAMCEVI, an additional 2 subjects (2/137; 1.5%) each exhibited 1 episode of transient post-suppression breakthrough (serum testosterone > 50 ng/dL). One subject showed 54.7 ng/dL on Day 170, while the other showed 61.4 ng/dL on Day 170 and 59.7 ng/dL on Day 171. Both subject's serum testosterone levels returned to castrate levels and stayed below through the remainder of the study.

Serum PSA levels were substantially reduced after the first injection, and this effect remained until the end of the study. In the ITT population, the PSA levels were lowered on average by

51% after 4 weeks (Day 28) after administration of CAMCEVI and lowered by 79% at the end of study (Day 336). Similar decreases in PSA levels were observed in the PP population.
PSA based results should always be interpreted with caution as they are not validated surrogate endpoints of clinical benefit in individual patients

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

General Toxicology
Published studies on a sustained release formulation of leuprolide demonstrated that the product has a low order of acute toxicity in mice and rats, with LD50's above 5000 mg/kg (greater than 400 mg/kg of leuprolide) for oral, subcutaneous and intraperitoneal routes of administration, and above 2000 mg/kg (greater than 160 mg/kg as leuprolide) for intramuscular injection. The only clinical signs observed were related to local effects at the site of injection.

3-Month Single Dose Subcutaneous Toxicity Study in Male Sprague-Dawley Rats
Leuprolide mesylate (6.8, 20.3 and 33.8 mg/body) was administered to 7-week-old male rats via single subcutaneous injection that resulted in sustained release of leuprolide over a 91-day period. Serum testosterone was suppressed to castrate level (≤50 ng/dL) throughout the study, with a fluctuation above castrate level at one timepoint observed in the low-dose group. No mortality or moribundity were noted in any of the leuprolide mesylate-treated groups or a reference leuprolide-treated group. A shortening of prothrombin time and decreases in the weight of the testis, epididymis, prostate, and seminal vesicles were observed in all leuprolide-treated groups. Pituitary hyperplasia was noted in all leuprolide-treated groups; compressed adjacent tissues were noted in one animal from the low-dose leuprolide mesylate group, and focal (nodular) hyperplasia with atypia was noted in one animal from the reference group. The no observed adverse effect level (NOAEL) of leuprolide mesylate was below 6.8 mg/body (approximately 20.4–25.8 mg/kg, or 4-5 times the recommended human dose based on body surface area), since pituitary hyperplasia noted at this level and higher was considered adverse.

6-Month Single Dose Subcutaneous Toxicity Study in Male Sprague-Dawley Rats
Leuprolide mesylate (6.8, 20.3 and 33.8 mg/body) was administered to 9-week-old male rats via single subcutaneous injection that resulted in sustained release of leuprolide over 182 days. Serum testosterone was suppressed to castrate levels (≤50 ng/dL) throughout the study, with fluctuations above castrate level at three timepoints observed in the low-dose group and one timepoint in the high-dose group. Focal hyperplasia and adenoma in the pituitary that contributed to pituitary enlargement, nodules or masses was observed in all leuprolide mesylate-treated groups and a reference leuprolide-treated group. One animal from the low-dose leuprolide mesylate group was terminated 2 days before end of study due to declined clinical condition primarily caused by such pituitary changes. Other leuprolide related changes

observed included reductions in the weight of male sex organs, heart, liver and kidney, food consumption, body weight, red blood cell counts and prothrombin time. Notable changes in serum biochemistry included reduced alkaline phosphatase and increased cholesterol. The NOAEL was below 6.8 mg/body (approximately 16.0-22.0 mg/kg) since the pituitary changes of hyperplasia and adenoma noted at this level and higher were considered to be adverse. At the dose of 6.8 mg/body, systemic exposure (AUC) was approximately 4 times the human exposure at the recommended dose. Local tolerance of leuprolide mesylate was also assessed in this study, and injection site inflammation was observed in some animals at the highest dose.

No studies with repeat administration were conducted. CAMCEVI is an extended-release formulation. Effects of continuous release were observed for a 6-month period.

Single Dose Subcutaneous Toxicity Studies in Dogs

A single SC injection (60 mg in 0.5 mL) of sustained release leuprolide or a supporting formulation in dogs showed no overt toxicities, no body weight abnormalities, and no remarkable observations at the injection sites during the study. In another study, dogs received a single SC injection (45 mg in 0.375 mL) of leuprolide or a supporting formulation. There were no body weight abnormalities during the study. Overt toxicity not related to the test article was observed in two dogs (i.e., seizures and otitis externa). Three dogs demonstrated minimal edema at the injection site on Day 1, and one dog had slight edema at the injection site on Day 14.

Carcinogenicity

No carcinogenicity studies have been conducted specifically with CAMCEVI.

Two-year carcinogenicity studies with leuprolide were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no pituitary abnormalities were observed at a dose as high as 60 mg/kg for 2 years.

Genotoxicity

No mutagenicity, clastogenicity or aneugenicity studies have been conducted specifically with CAMCEVI.

A sustained release formulation of leuprolide was not genotoxic in either an in vitro cytogenetics assay using Chinese hamster lung cells, an in vivo micronucleus assay in mice, or the Ames test with five strains of *Salmonella typhimurium*.

Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies have been conducted specifically with CAMCEVI.

Reproduction and teratology studies conducted with a sustained release formulation indicate all effects observed are related to consequences of repeated administration of this pharmacologic agent. Fertility studies, where male rats were dosed once every four weeks for three doses prior to mating, showed that the drug produced reversible atrophy of the testes or accessory sex organs at doses as low as 0.024 mg/kg (as leuprolide), and a decrease in LH, FSH and testosterone levels. A reversible decrease in copulation and implantation sites was also observed at the high dose of 2.4 mg/kg. No effects on the fetuses were observed.

Female rats dosed at 2.4 mg leuprolide acetate/kg once, four weeks prior to mating, caused an interruption in the estrus cycle and decreased vaginal size. Weights of the ovaries and uterus were decreased. Following mating, corpora lutea and the number of implantation sites were decreased at 0.24 mg/kg and above; the number of live fetuses was reduced at 2.4 mg/kg and above. No abnormal development was noted in the fetuses.

In the perinatal study, the administration of the sustained release formulation of leuprolide in rats prior to delivery at up to 8 mg/kg showed effects on sex organ weights, but no adverse effects on the fetuses, including weights of their sex organs.

Major fetal malformations were observed in developmental and reproductive toxicology studies in rabbits after a single administration of a monthly formulation of leuprolide administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (approximately 1/1500 to 1/15 the human dose based on body surface area using an estimated daily dose in animals and humans). Since a depot formulation was utilized in the study, a sustained exposure to leuprolide was expected throughout the period of organogenesis and to the end of gestation. Increased fetal mortality and decreased fetal weights with the two higher doses were observed.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]CAMCEVI®
Leuprolide injectable emulsion

Read this carefully before you start taking **CAMCEVI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CAMCEVI**.

Serious Warnings and Precautions

CAMCEVI should be prescribed by a doctor experienced with the use of hormonal therapy in prostate cancer.

CAMCEVI may cause:

- Worsening of the symptoms of prostate cancer at the beginning of the treatment. CAMCEVI may cause an increase in blood levels of testosterone during the first week of treatment. This can cause:
  - bone pain, numbness, tingling, muscle weakness
  - bloody urine
  - blockage of your urinary tract or bladder
  - pressure on your spinal cord (spinal cord compression)
- **Pituitary apoplexy** (bleeding or decreased blood flow causing tissue death of the pituitary gland). This might occur within 2 weeks of the first dose, and some within the first hour.
- **Osteoporosis** (bone thinning). CAMCEVI may increase your risk of osteoporosis and bone fractures. Your healthcare professional will monitor your risks for bone thinning and bone fractures during treatment with CAMCEVI.

See the **Serious side effects and what to do about them table**, below, for more information on these and other serious side effects.

What is CAMCEVI used for?
CAMCEVI is used for the treatment of adult patients with advanced prostate cancer.

How does CAMCEVI work?
CAMCEVI belongs to a group of medicines called Gonadotropin Releasing Hormone (GnRH) analogues.

CAMCEVI contains leuprolide. It works by blocking the action of androgens (hormones like testosterone). This will shrink or stop the growth of prostate cancer cells which may result in reduced symptoms related to the disease.

What are the ingredients in CAMCEVI?
Medicinal ingredients: Leuprolide mesylate
Non-medicinal ingredients: N-methylpyrrolidone; Poly (D, L-lactide).

CAMCEVI comes in the following dosage forms:
Extended release emulsion: 42 mg leuprolide (as leuprolide mesylate) in a pre-filled syringe.

Do not use CAMCEVI if:

- you are allergic to leuprolide mesylate or any other ingredients in CAMCEVI.
- you have had an allergic reaction to CAMCEVI or other drugs like CAMCEVI, including a severe allergic reaction (anaphylactic shock).
- you are a woman.
- you are pregnant or may become pregnant. Leuprolide may cause miscarriage or may cause harm to an unborn baby.
- you are breast-feeding.
- you are younger than 18 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CAMCEVI. Talk about any health conditions or problems you may have, including if you:

- have a history of urinary tract obstruction.
- have had spread of cancer to the bones of the spine (vertebrae).
- have a history of spinal cord compression.
- have risk factors for bone thinning (osteoporosis), such as if you:
  - have a family history of severe osteoporosis
  - have low bone mineral density
  - are taking any medication that can cause thinning of the bones. For example, corticosteroids or anti-convulsive (anti-seizure) medications
  - use alcohol or tobacco.
- have heart disease, or a genetic heart condition called "Long QT syndrome".

Other warnings you should know about:

CAMCEVI can cause serious side effects, including:

- **Cardiovascular problems**, such as: heart attack, sudden cardiac death (sudden loss of heart function) and stroke. It may also cause changes to your heart rhythm.
- **Hyperglycemia** (increase in blood sugar) and **Diabetes** (high blood sugar).
  - CAMCEVI may increase your blood sugar levels. This may increase your risk of diabetes or worsen the symptoms in patients with diabetes.
  - If you have diabetes, talk to your doctor before you are given CAMCEVI. You may need to test your blood sugar more frequently during treatment.
  - Your healthcare professional may need to give or change your blood sugar medicine. This will help control your blood sugar levels.
- **Anemia** (decreased number of red blood cells)
  - CAMCEVI suppresses the production of testosterone. This may cause a decrease in the number of red blood cells (anemia).
  - If you have anemia, talk to your doctor before you are given CAMCEVI.
- **Convulsions**.
- **Pneumonitis** (inflammation of the lung tissue).

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Hypogonadism (reduced production of sex hormone)
Treatment with CAMCEVI may reduce the production of male sex hormones. This can lead to side effects such as loss of sexual desire and inability to maintain erection (impotence).

Fertility
Treatment with CAMCEVI may decrease your ability to have children. Talk to your doctor if this is a concern for you.

Monitoring and laboratory tests
Your healthcare professional will regularly monitor and assess your health while you are being treated with CAMCEVI. This may include blood tests, urine tests, bone scans (such as ultrasonography and/or CT scan) and ECG recording.

Driving and using machines
CAMCEVI can cause fatigue and dizziness. Before you drive or do tasks that require special attention, wait until you know how you respond to CAMCEVI.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CAMCEVI:
- antiarrhythmic drugs (used to treat abnormal heart rhythm) such as: quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, dronedarone, flecainide, propafenone
- antipsychotic drugs (used to treat mental disorders) such as: chlorpromazine
- antidepressant drugs (used to treat depression) such as: amitrptyline, nortryptiline
- opioid drugs (used to treat pain), such as methadone
- antibiotics (used to treat bacterial infections), such as: erythromycin, clarithromycin, azithromycin, moxifloxacin
- antifungals (used to treat fungal infections)
- antimalarials (used to treat malaria), such as quinine
- drugs belonging to a class called beta-2 agonists (used to treat asthma), such as salbutamol
- drugs belonging to a class called 5-HT3 antagonists (used to treat nausea), such as ondansetron

How to take CAMCEVI:
CAMCEVI will be given to you by a healthcare professional in a healthcare setting. CAMCEVI is given by injection under the skin (subcutaneously).

Usual dose:
42 mg once every 6 months.

Overdose:
If you think you, or a person you are caring for, have been given too much CAMCEVI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
It is very important that you keep all scheduled appointments with your doctor. If you miss an appointment by a few days, it should not disrupt the benefits of treatment. But you must follow your drug administration schedules for the therapy to be effective.

If you miss an appointment to receive your dose of CAMCEVI, contact your health professional as soon as possible.

What are possible side effects from using CAMCEVI?
These are not all the possible side effects you may have when taking CAMCEVI. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:
- hot flash
- skin reaction at injection site (ex. burning and stinging, pain, redness, itching and/or swelling)
- fatigue
- pain in muscles, ligaments, tendons or bones (musculoskeletal pain)
- pain in extremity
- joint pain
- regularly waking up at night to urinate (nocturia)
- urinary urgency
- dizziness
- upper respiratory tract infection (such as a cold)

If any of the above symptoms affects you severely, contact your healthcare professional.

CAMCEVI may cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Hypertension (high blood pressure): severe headaches, nosebleed, vision problems, shortness of breath, fatigue or confusion, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		✓	
COMMON			
Osteoporosis (thin, fragile bones): broken bones, pain, back pain that gets worse when standing or walking		✓	
Prolongation of QT interval (a heart rhythm condition): Irregular heartbeat, fainting, loss of consciousness, seizures			✓
Subdural haematoma (bleeding within the skull): headache that doesn't go away; drowsiness; confusion, memory changes; speech or language problems;			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
paralysis, loss of consciousness			
Tumor flare (worsening of the symptoms of prostate cancer at the beginning of the treatment): increase in the severity of side effects or new pain after starting hormone therapy		✓	
UNCOMMON			
Atrial fibrillation (abnormal heart rhythm which is rapid and irregular): chest discomfort with unpleasant awareness of your heartbeat, faintness, shortness of breath, weakness			✓
Deep vein thrombosis (blood clot in the deep veins of the leg or arm): swelling, pain, arm or leg may be warm to the touch and may appear red			✓
Diabetes: with symptoms such as excessive thirst, excessive urination, excessive eating, unexplained weight loss, poor wound healing, infections		✓	
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		✓	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			✓
VERY RARE			
Pituitary apoplexy (bleeding or decreased blood flow to your pituitary gland): sudden headache, vomiting, visual changes			✓
UNKNOWN			
Anemia (decreased number of red blood cells): fatigue, loss of energy, looking pale, shortness of breath, weakness		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Convulsion: seizure, spasms, shaking or fits			✓
Pneumonitis (inflammation of the lung tissue): shortness of breath, cough, fatigue, loss of appetite, unintentional weight loss			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
CAMCEVI will be managed and stored by healthcare professionals. The information below on how to store CAMCEVI is meant for your healthcare professional.

CAMCEVI should be stored refrigerated between 2°C to 8°C (36-46°F). Do NOT freeze.
Store in the original package and protect from light.

Keep out of reach and sight of children.

If you want more information about CAMCEVI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling Accord Healthcare Inc. at 1-866-296-0354.

This leaflet was prepared by: Accord Healthcare Inc.

Last Revised: November 12, 2021