

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CAMCEVI ETM® and CAMCEVI® safely and effectively. See full prescribing information for CAMCEVI ETM or CAMCEVI.

CAMCEVI ETM (leuprolide) injectable emulsion, for subcutaneous use

CAMCEVI (leuprolide) injectable emulsion, for subcutaneous use

Initial U.S. Approval: 2021

----- INDICATIONS AND USAGE -----

CAMCEVI ETM and CAMCEVI are gonadotropin-releasing hormone (GnRH) agonists indicated for the treatment of adult patients with advanced prostate cancer. (1)

----- DOSAGE AND ADMINISTRATION -----

- CAMCEVI ETM and CAMCEVI have different strengths and dosages. Ensure the correct formulation is being prescribed, dispensed, and administered. (2.1)
- Recommended Dosage:
 - CAMCEVI ETM: 21 mg subcutaneously every 3 months. (2.1)
 - CAMCEVI: 42 mg subcutaneously every 6 months. (2.1)
- See Full Prescribing Information for instructions on preparation and administration of the pre-filled syringe. (2.2)

----- DOSAGE FORMS AND STRENGTHS -----

- Injectable emulsion:
 - CAMCEVI ETM: 21 mg of leuprolide in a single-dose, pre-filled syringe (3)
 - CAMCEVI: 42 mg of leuprolide in a single-dose, pre-filled syringe (3)

----- CONTRAINDICATIONS -----

- Hypersensitivity to GnRH, GnRH agonist analogs, or any of the components of CAMCEVI ETM or CAMCEVI. (4)

----- WARNINGS AND PRECAUTIONS -----

- Tumor Flare: Transient worsening of bone pain, ureteral obstruction, spinal cord compression, or the occurrence of additional signs and symptoms of prostate cancer may develop during the first few weeks of treatment. Monitor patients closely and manage symptoms. (5.1)
- Hyperglycemia and Diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Monitor blood glucose levels and manage according to current clinical practice. (5.2)
- Cardiovascular Diseases: Increased risk of myocardial infarction, sudden cardiac death, and stroke has been

reported in men receiving GnRH agonists. Monitor for cardiovascular disease and manage according to current clinical practice. (5.3)

- QT/QTc Prolongation: Androgen deprivation therapy may prolong the QT interval. Consider periodic monitoring of electrocardiograms and electrolytes. (5.4)
- Convulsions: Manage convulsions according to the current clinical practice. (5.5)
- Severe Cutaneous Adverse Reactions: CAMCEVI ETM and CAMCEVI can cause severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). Interrupt CAMCEVI ETM or CAMCEVI if signs or symptoms of SCARs develop. Permanently discontinue if SCARs are confirmed. (5.6)
- Embryo-Fetal Toxicity: CAMCEVI ETM and CAMCEVI may cause fetal harm. (5.8, 8.1)

----- ADVERSE REACTIONS -----

CAMCEVI ETM 21 mg for 3-month administration:

The most common ($\geq 5\%$) adverse reactions, including laboratory abnormalities, were increased triglycerides, increased alanine aminotransferase, hot flush, hypertension, decreased hemoglobin, increased sodium, increased aspartate aminotransferase, injection site reaction, weight increase, increased potassium, decreased neutrophils, and decreased white blood cells. (6.1)

CAMCEVI 42 mg for 6-month administration:

The most common ($\geq 5\%$) adverse reactions were hot flushes, hypertension, injection site reactions, fatigue, upper respiratory tract infections, musculoskeletal pain, pain in extremity, arthralgia, micturition urgency, nocturia, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Accord BioPharma Inc. at 1-866-941-7875 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----- USE IN SPECIFIC POPULATIONS -----

- Females and males of reproductive potential: CAMCEVI ETM and CAMCEVI may impair fertility. (8.3)
- Safety and effectiveness in pediatric patients have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended dosage

- 2.2 Preparation and Administration
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Tumor Flare
 - 5.2 Hyperglycemia and Diabetes
 - 5.3 Cardiovascular Diseases
 - 5.4 QT/QTc Prolongation
 - 5.5 Convulsions
 - 5.6 Severe Cutaneous Adverse Reactions
 - 5.7 Laboratory Tests
 - 5.8 Embryo-Fetal Toxicity
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trial Experience
 - 6.2 Postmarketing Experience
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy

- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CAMCEVI ETM and CAMCEVI are indicated for the treatment of adult patients with advanced prostate cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

CAMCEVI ETM and CAMCEVI have different strengths and dosages. Check the product label to ensure that the correct strength (CAMCEVI ETM or CAMCEVI) is being prescribed, dispensed, and administered.

Administer CAMCEVI ETM and CAMCEVI by subcutaneous injection.

The recommended dosages are presented in Table 1.

Table 1: Recommended Dosage

Product	Recommended Dosage
CAMCEVI ETM	21 mg every 3 months
CAMCEVI	42 mg every 6 months

In patients treated with GnRH analogues for prostate cancer, treatment is usually continued upon development of metastatic castration-resistant prostate cancer.

2.2 Preparation and Administration

CAMCEVI ETM and CAMCEVI must be administered by a healthcare provider.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

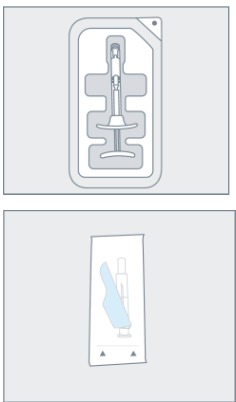
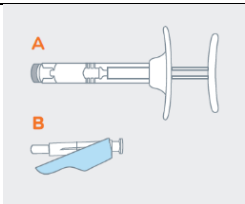
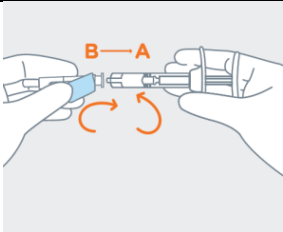
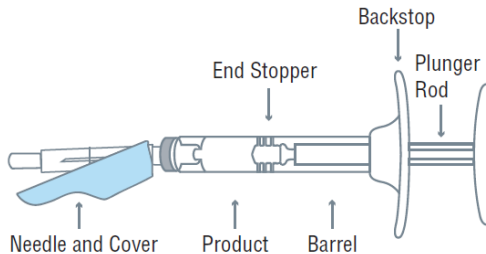
Important: Read the instructions completely prior to administration. Do NOT substitute any of the components from the kit for administration.

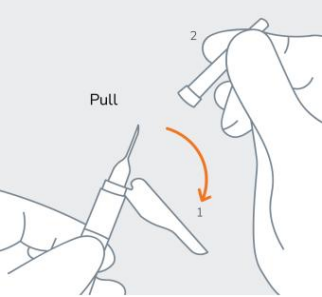
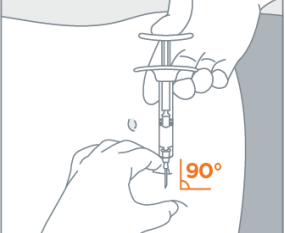
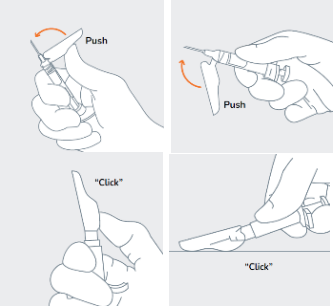
CAMCEVI ETM and CAMCEVI are packaged in a blister in the kit. Check to make sure the kit contains:

- One sterile, single-dose pre-filled syringe with plunger rod and backstop
- One sterile 18-gauge SurGuard®3 safety needle, 5/8-inch needle
- Prescribing Information

Follow the detailed instructions to ensure correct preparation of CAMCEVI ETM or CAMCEVI prior to administration:

	STEP 1 Remove CAMCEVI ETM or CAMCEVI kit from refrigerator.
--	---

	Keep the contents in their original, sealed blister carton and allow to sit at room temperature for 30 minutes before use. Return to refrigerator after 30 minutes if not used.
	STEP 2 On a clean, dry surface, open carton and remove the contents. Examine all contents of the package. Do not use if any component is damaged. Check the expiration date on the syringe. Do not use if the expiration date has passed. The use of gloves is recommended during syringe assembly and administration.
	STEP 3 Remove pre-filled syringe (A) from the blister tray and open the safety needle (B) package by peeling back the paper tab. The safety needle (B) package is located beneath the blister tray. Visually inspect the syringe for particulate matter prior to administration. The emulsion should appear off-white to pale yellow, viscous, and opalescent. Do not use if particulate matter is observed prior to administration.
	STEP 4 Remove the gray cap from the syringe (A). Attach the needle (B) to the end of the syringe (A) by gently screwing clockwise with approximately a three-quarter turn until the needle is secure. Do not overtighten, as the needle hub may become damaged resulting in leakage of the product during injection. The safety sheath may also be damaged if the needle is overtightened onto the syringe. See figure of assembled pre-filled syringe below. 

	STEP 5 Choose an injection site on the upper- or mid-abdominal area with sufficient soft or loose subcutaneous tissue 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). In addition, avoid applying heat directly to the site of injection.
	STEP 6 (1) Move the safety sheath away from the needle and towards the syringe and (2) remove the clear needle cover immediately before injection. Note: Should the needle hub appear to be damaged, or leak, the product should NOT be used. The damaged needle should NOT be replaced and the product should NOT be injected. In the event of damage to the needle hub, use a new replacement CAMCEVI ETM or CAMCEVI kit.
	STEP 7 Use standard aseptic technique when performing the injection. Grab and bunch the skin around the injection site with one hand. Insert the needle at a 90° angle to the skin surface, and then release the bunched skin.
	STEP 8 Inject the full contents of the syringe with a slow and steady push on the plunger, and then withdraw the needle at the same 90° angle used for insertion.
	STEP 9 Immediately following the withdrawal of the needle, activate the safety sheath using a finger/thumb or flat surface and push until it completely covers the needle tip and locks into place. An audible and tactile “click” verifies a locked position. Check to confirm the safety sheath is fully engaged.
	STEP 10

	After use, discard all components safely in a suitable sharps container. Dispose of the syringe and contaminated products according to local regulations/procedures.
--	--

3 DOSAGE FORMS AND STRENGTHS

Injectable emulsion:

CAMCEVI ETM

- 21 mg leuprolide (equivalent to approximately 24 mg leuprolide mesylate) as a sterile, off-white to pale yellow, viscous, and opalescent emulsion in a single-dose, pre-filled syringe for subcutaneous injection.

CAMCEVI

- 42 mg leuprolide (equivalent to approximately 48 mg leuprolide mesylate) as a sterile, off-white to pale yellow, viscous, and opalescent emulsion in a single-dose, pre-filled syringe for subcutaneous injection.

4 CONTRAINDICATIONS

CAMCEVI ETM and CAMCEVI are contraindicated in patients known to be hypersensitive to GnRH, GnRH agonist analogs, or any of the excipients in CAMCEVI ETM or CAMCEVI. Anaphylactic reactions to GnRH agonist analogs have been reported in medical literature.

5 WARNINGS AND PRECAUTIONS

5.1 Tumor Flare

CAMCEVI ETM and CAMCEVI, like other GnRH agonists, cause 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 develop during the first few weeks of CAMCEVI ETM or CAMCEVI treatment. Patients treated with CAMCEVI ETM or CAMCEVI may experience a temporary increase in bone pain, which can be managed symptomatically.

Cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

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

5.2 Hyperglycemia and Diabetes

Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent the development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes.

5.3 Cardiovascular Diseases

Increased risk of developing myocardial infarction, sudden cardiac death, and stroke has been reported in association with use of GnRH agonists in men. Evaluate patients for cardiovascular risk factors. Monitor for symptoms and signs suggestive of development of cardiovascular disease and manage according to current clinical practice.

5.4 QT/QTc Prolongation

Androgen deprivation therapy can prolong the QT/QTc interval. Consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Correct electrolyte abnormalities. Consider periodic monitoring of electrocardiograms and electrolytes.

5.5 Convulsions

Convulsions have been reported in patients receiving GnRH agonists, including CAMCEVI ETM or CAMCEVI [see *Adverse Reactions* (6.2)]. Manage patients receiving a GnRH agonist who experience convulsions according to current clinical practice.

5.6 Severe Cutaneous Adverse Reactions

CAMCEVI ETM and CAMCEVI can cause severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). SCARs, including SJS/TEN, DRESS, and AGEP, occurred in patients receiving CAMCEVI ETM or CAMCEVI or other GnRH agonists; including cases with visceral involvement and/or requiring skin grafts [see *Adverse Reactions* (6.2)].

Monitor patients for the development of SCARs.

If a SCAR is suspected, interrupt CAMCEVI ETM or CAMCEVI until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, or for other Grade 4 skin reactions, permanently discontinue CAMCEVI ETM or CAMCEVI.

5.7 Laboratory Tests

Monitor serum levels of testosterone following injection of CAMCEVI ETM or CAMCEVI. In the majority of patients treated with CAMCEVI ETM or CAMCEVI, testosterone levels increased above baseline during the first week, and then declined thereafter to castration levels (<50 ng/dL) within 4 weeks [see *Adverse Reactions* (6) and *Clinical Studies* (14)].

5.8 Embryo-Fetal Toxicity

Based on findings in animal studies and mechanism of action, CAMCEVI ETM and CAMCEVI can cause fetal harm when administered to a pregnant woman. In animal developmental and reproductive toxicology studies, administration of a monthly formulation of leuprolide on day 6 of pregnancy (sustained exposure was expected throughout the period of organogenesis) caused adverse embryo-fetal toxicity in animals at doses less than the human dose based on body surface area using an estimated

daily dose. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus [see *Use in Specific Populations (8.1)*, *Clinical Pharmacology (12.1)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Tumor Flare [see *Warnings and Precautions (5.1)*]
- Hyperglycemia and Diabetes [see *Warnings and Precautions (5.2)*]
- Cardiovascular Diseases [see *Warnings and Precautions (5.3)*]
- QT/QTc Prolongation [see *Warnings and Precautions (5.4)*]
- Convulsions [see *Warnings and Precautions (5.5)*]
- Severe Cutaneous Adverse Reactions [See *Warnings and Precautions (5.6)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

FP01C-17-001 (CAMCEVI ETM 21 mg for 3-Month Administration):

The safety of CAMCEVI ETM was evaluated in an open-label, single arm, clinical trial (FP01C-17-001), patients with advanced prostate cancer received CAMCEVI ETM administered subcutaneously at a dose of 21 mg on Day 0 and Day 84 [see *Clinical Studies (14)*]. Of 144 patients enrolled, 132 (92%) received both doses of CAMCEVI ETM.

Serious adverse reactions occurred in 6% of patients who received CAMCEVI ETM. Serious adverse reactions included acute myocardial infarction, cerebrovascular accident, drug induced liver injury, and pancreatitis (each 0.7%).

Permanent discontinuation of CAMCEVI ETM due to an adverse reaction occurred in 0.7% of patients (stroke).

The most common ($\geq 5\%$) adverse reactions, including laboratory abnormalities, were increased triglycerides, increased alanine aminotransferase, hot flush, hypertension, decreased hemoglobin, increased sodium, increased aspartate aminotransferase, injection site reaction, weight increase, increased potassium, decreased neutrophils, and decreased white blood cells.

Table 2 summarizes the most common ($\geq 5\%$) adverse reactions in FP01C-17-001.

Table 2. Adverse Reactions Occurring in $\geq 5\%$ of Patients - FP01C-17-001

Adverse Reaction	All Grades N = 144 (%)	Grade 3-4 ^a N = 144 (%)
------------------	------------------------------	--

Hot flush	24	0
Hypertension ^a	15	0.7
Injection site reaction ^b	10	0
Weight increase	8	0

^a Only includes a grade 3 adverse reaction. Hypertension includes blood pressure increased, essential hypertension, and hypertension.

^b Injection site reaction includes injection site erythema, hemorrhage, induration, nodule, localized edema; and injection site pain.

Clinically relevant adverse reactions in < 5% of patients who received CAMCEVI ETM included insomnia, acute myocardial infarction, cerebrovascular accident, diabetes mellitus, decreased libido, and electrocardiogram QT prolonged.

Table 3 summarizes laboratory abnormalities in FP01C-17-001.

Table 3. Laboratory Abnormalities Occurring in ≥5% of Patients - FP01C-17-001

Laboratory Abnormality	All Grades N = 144 (%)	Grade 3-4 ^a N = 144 (%)
Chemistry		
Increased triglycerides	44	1.4
Increased alanine aminotransferase	28	0.7
Increased sodium	13	0
Increased aspartate aminotransferase	13	0
Increased potassium	7	0
Hematology		
Decreased hemoglobin	15	0
Decreased neutrophils	6	0
Decreased white blood cells	6	0

^a Only includes a grade 3 adverse reaction.

FP01C-13-001 (CAMCEVI 42 mg for 6-Month Administration):

The safety of CAMCEVI was evaluated in an open-label, single-arm, international clinical trial (FP01C-13-001) in patients with advanced prostate cancer. Patients 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.

Serious adverse reactions occurred in 15% of patients who received CAMCEVI, including 1% of patients who experienced subdural hematoma. Fatal adverse reactions occurred in 2% of patients, including cerebrovascular accident (0.7%) and pulmonary embolism (0.7%).

The most common adverse reactions ($\geq 5\%$) occurring during a median follow-up duration of 336 days were hot flush, hypertension, injection site reactions, upper respiratory tract infections, musculoskeletal pain, fatigue, pain in extremity, arthralgia, micturition urgency, nocturia, and dizziness.

Table 4 summarizes the adverse reactions in FP01C-13-001.

Table 4. Adverse Reactions Occurring in $\geq 5\%$ of CAMCEVI in Advanced Prostate Cancer Patients - FP01C-13-001

Adverse Reaction	CAMCEVI N = 137	
	All Grades (%)	Grade 3-4 (%)
Vascular disorders		
Hot flushes ^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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of leuprolide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

During postmarketing surveillance, which includes other dosage forms and other patient populations, the following adverse reactions were reported.

Allergic Conditions: anaphylactoid or asthmatic process, rash, urticaria, hypersensitivity reactions including anaphylaxis, and photosensitivity reactions

Cardiovascular System: hypotension

Central/Peripheral Nervous System: convulsion, peripheral neuropathy, spinal fracture/paralysis

Endocrine System: pituitary apoplexy

Hepato-biliary disorder: drug-induced liver injury

Psychiatric: mood swings, including depression, suicidal ideation and attempt

Respiratory, thoracic and mediastinal disorder: interstitial lung disease

Musculoskeletal System: decreased bone density, tenosynovitis-like symptoms, fibromyalgia

Skin and Subcutaneous: injection site reactions, SJS/TEN, DRESS, AGEP, dermatitis exfoliative, bullous dermatitis, and erythema multiforme

Urogenital System: prostate pain

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies and mechanism of action, CAMCEVI ETM and CAMCEVI can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies, administration of a monthly formulation of leuprolide on day 6 of pregnancy (sustained exposure was expected throughout the period of organogenesis) caused adverse embryo-fetal toxicity in animals at doses less than the human dose based on body surface area using an estimated daily dose (see *data*). Advise pregnant patients and females of reproductive potential of the potential risk to the fetus.

Data

Animal Data

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. Similar studies in rats did not demonstrate an increase in fetal malformations, however, there was increased fetal mortality and decreased fetal weights with the two higher doses of the monthly formulation of leuprolide in rabbits and with the highest dose in rats.

8.2 Lactation

Risk Summary

The safety and efficacy of CAMCEVI ETM and CAMCEVI have not been established in females. There is no information regarding the presence of leuprolide in human milk, the effects on the breast-fed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in a breastfed child, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Females and Males of Reproductive Potential

Infertility

Males

Based on findings in animals and mechanism of action, CAMCEVI ETM and CAMCEVI may impair fertility in males of reproductive potential [see *Clinical Pharmacology (12.1)*, *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and efficacy of CAMCEVI ETM and CAMCEVI in pediatric patients have not been established.

8.5 Geriatric Use

CAMCEVI ETM 21 mg for 3-Month Administration:

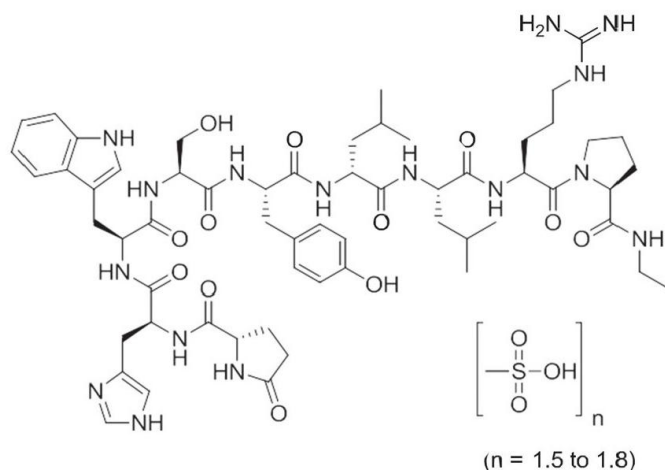
Of the 144 patients who received CAMCEVI ETM in the FP01C-17-001, 74% were 65 years of age or older, while 31% were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients over the age of 65 and younger patients.

CAMCEVI 42 mg for 6-Month Administration:

Of the 137 patients who received CAMCEVI in the FP01C-13-001 study, 74% were 65 years of age or older, while 37% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

11 DESCRIPTION

Leuprolide mesylate is a synthetic nonapeptide analog of naturally occurring GnRH and is a GnRH agonist. The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide mesylate (salt) with the following structural formula. The pH of 50 mg/mL solution of leuprolide mesylate in water is approximately 5.7.



CAMCEVI ETM 21 mg for 3-Month Administration:

CAMCEVI ETM is a sterile formulation of leuprolide mesylate for subcutaneous injection. CAMCEVI ETM is designed to deliver approximately 21 mg of leuprolide over 3 months.

CAMCEVI ETM is supplied as a kit with a pre-filled, single-dose, sterile syringe for subcutaneous injection. Each pre-filled syringe delivers 21 mg leuprolide (equivalent to approximately 24 mg leuprolide mesylate), poly (D, L-lactide-co-Glycolide) (160 mg) polymer and *N*-methyl-2-pyrrolidone (116 mg).

CAMCEVI 42 mg for 6-Month Administration:

CAMCEVI is a sterile formulation of leuprolide mesylate for subcutaneous injection. CAMCEVI is designed to deliver approximately 42 mg of leuprolide over 6 months.

CAMCEVI is supplied as a kit with a pre-filled, single-dose, sterile syringe for subcutaneous injection. Each pre-filled syringe delivers 42 mg leuprolide (equivalent to approximately 48 mg leuprolide mesylate), poly (D, L-lactide) (184 mg) polymer and *N*-methyl-2-pyrrolidone (136 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide, a GnRH agonist, acts as an inhibitor of gonadotropin secretion. 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.

12.2 Pharmacodynamics

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). However, continuous daily administration of leuprolide results in decreased levels of LH and FSH. In males, testosterone is reduced to below castration levels. These decreases generally occur within 2 to 4 weeks after initiation of treatment, and castration levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to 5 years.

CAMCEVI ETM 21 mg for 3-Month Administration:

Mean serum testosterone concentrations transiently increased, then fell to below castrate threshold levels (< 50 ng/dL) within 4 weeks following administration of the dose of leuprolide, and generally remained below castrate threshold levels throughout treatment.

CAMCEVI 42 mg for 6-Month Administration:

Mean serum testosterone concentrations transiently increased, then fell to below castrate threshold levels (≤ 50 ng/dL) within 3 weeks following administration of the dose of leuprolide, and generally remained below castrate threshold levels throughout treatment.

12.3 Pharmacokinetics

CAMCEVI ETM 21 mg for 3-Month Administration:

Leuprolide concentration is variable, exhibiting an initial rapid increase followed by a rapid decline over the first 3 days before reaching steady concentrations for the duration of the dosing interval. The mean serum leuprolide $C_{\max}$ was 34.8 ng/mL following the first dose and 32.6 ng/mL following the second dose of CAMCEVI ETM. The mean serum leuprolide concentration was maintained at 0.32 – 1.91 ng/mL after Day 3 following the first dose and maintained at 0.23 – 2.02 ng/mL after Day 3 following the second dose. The mean $AUC_{0-3 \text{ mon}}$ was 80.1 day.ng/mL following the first dose and 92.9 day.ng/mL following the second dose of CAMCEVI ETM.

CAMCEVI 42 mg for 6-Month Administration:

Leuprolide concentration is variable, exhibiting an initial rapid increase followed by a rapid decline over the first 3 days before reaching steady concentrations for the duration of the dosing interval. The mean serum leuprolide $C_{\max}$ was 94.5 and 99 ng/mL following the first and second doses of CAMCEVI, respectively. The mean serum concentration was maintained at 0.497–2.57 and 0.507–2.39 ng/mL after Day 3 following the first and second doses, respectively. The mean $AUC_{0-6 \text{ mon}}$ was 224 and 268 day.ng/mL following the first and second doses of CAMCEVI, respectively.

Absorption

CAMCEVI ETM 21 mg for 3-Month Administration:

The median $T_{\max}$ of leuprolide was 4 hours following the first and second doses of CAMCEVI ETM.

CAMCEVI 42 mg for 6-Month Administration:

The median $T_{\max}$ of leuprolide was 3.2 and 2.1 hours following the first and second doses of CAMCEVI, respectively.

Distribution

The mean steady-state volume of distribution of leuprolide was 27 L following an intravenous bolus in healthy male volunteers. Protein binding of leuprolide ranged from 43% to 49% in vitro.

Elimination

The mean systemic clearance was 7.6 L/h and terminal elimination half-life of approximately 3 hours following an intravenous bolus of leuprolide in healthy male volunteers.

Metabolism

Administration of radiolabeled leuprolide was metabolized to smaller inactive peptides which may then be further catabolized.

Excretion

Excretion of leuprolide has not been evaluated with CAMCEVI ETM or CAMCEVI.

Specific Populations

CAMCEVI ETM 21 mg for 3-Month Administration:

No clinically significant differences in the systemic exposure of leuprolide were observed based on age (51 to 89 years), race (White, Asian), or body weight (54 to 119 kg). The effect of renal or hepatic impairment on the pharmacokinetics of leuprolide has not been evaluated.

CAMCEVI 42 mg for 6-Month Administration:

No clinically significant differences in the systemic exposure of leuprolide were observed based on age (51 to 88 years), race/ethnicity (White, Black, Asian), or body weight (54 to 134 kg). The effect of renal or hepatic impairment on the pharmacokinetics of leuprolide has not been evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted with leuprolide 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. Patients have been treated with leuprolide for up to 3 years with doses as high as 10 mg/day and for 2 years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide using bacterial and mammalian systems. These studies provided no evidence of mutagenic potential.

Leuprolide may reduce male and female fertility. Administration of leuprolide to male and female rats at doses of 0.024, 0.24, and 2.4 mg/kg as monthly depot formulation for up to 3 months (approximately as low as 1/30 of the human dose based on body surface area using an estimated daily dose in animals and humans) caused atrophy of the reproductive organs, and suppression of reproductive function. These changes were reversible upon cessation of treatment.

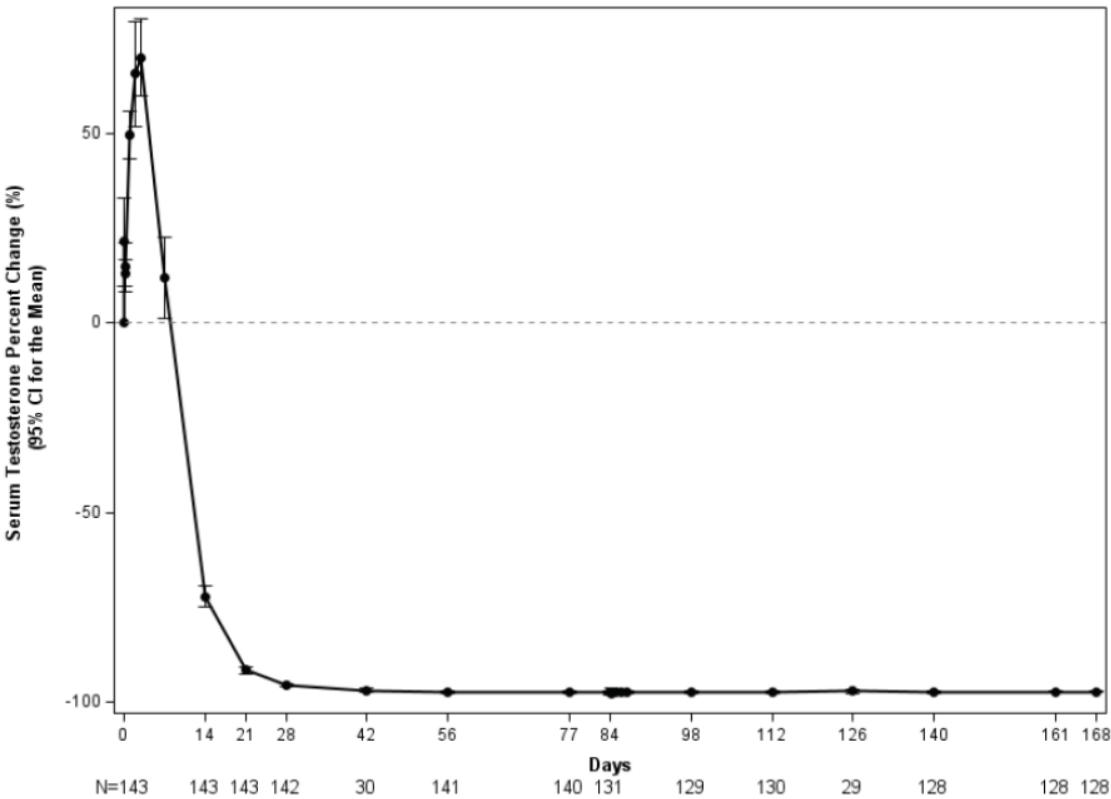
FP01C-17-001 (CAMCEVI ETM 21 mg for 3-Month Administration):

The efficacy of CAMCEVI ETM was evaluated in an open label, single arm, multinational study FP01C-17-001 (NCT03261999) in patients with advanced prostate carcinoma who have a screening morning serum testosterone level >150 ng/dL and Eastern Cooperative Oncology Group performance status ≤ 2 . CAMCEVI ETM was administered subcutaneously at a dose of 21 mg initially on Day 0 and on Week 12.

The population (n = 144) had a median age of 70 years (range 51 to 89) and was 88% White, 11% Asian, and 1% Black. Disease stage was distributed as follows: 5% metastatic (M1), 41% locally advanced (T3/4 NX M0 or any T N1 M0), 30% localized (T1 or T2 N0 M0), and 24% not classifiable.

The major efficacy outcome measure was medical castration rate, defined as achieving and maintaining serum testosterone suppression to < 50 ng/dL by Week 4 through Week 24 of treatment. Following the first injection of CAMCEVI ETM, serum testosterone levels were suppressed to < 50 ng/dL by Week 4 (+/-1day) in 97.9% of the patients; and from Week 4 through Week 24 in 97.2% of patients (95% CI: 92.7- 98.9) estimated using the Kaplan-Meier method. The time course of change from baseline in testosterone suppression are shown in Figure 1. The percentage of patients with testosterone suppression to < 20 ng/dL was 70.8% on Day 28.

Figure 1 CAMCEVI ETM Mean (95% CI) Percentage Change from Baseline in Serum Testosterone Concentration Over Time



Note: 1 subject with baseline testosterone value < 0.05 ng/mL was excluded from analysis.

In the clinical trial, PSA levels were monitored and were lowered on average by 48% 4 weeks after administration of CAMCEVI ETM, 88% after 3 months and remained suppressed throughout the 24 weeks of treatment. These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied. No evidence has shown that the rapidity of PSA decline correlates with clinical benefit.

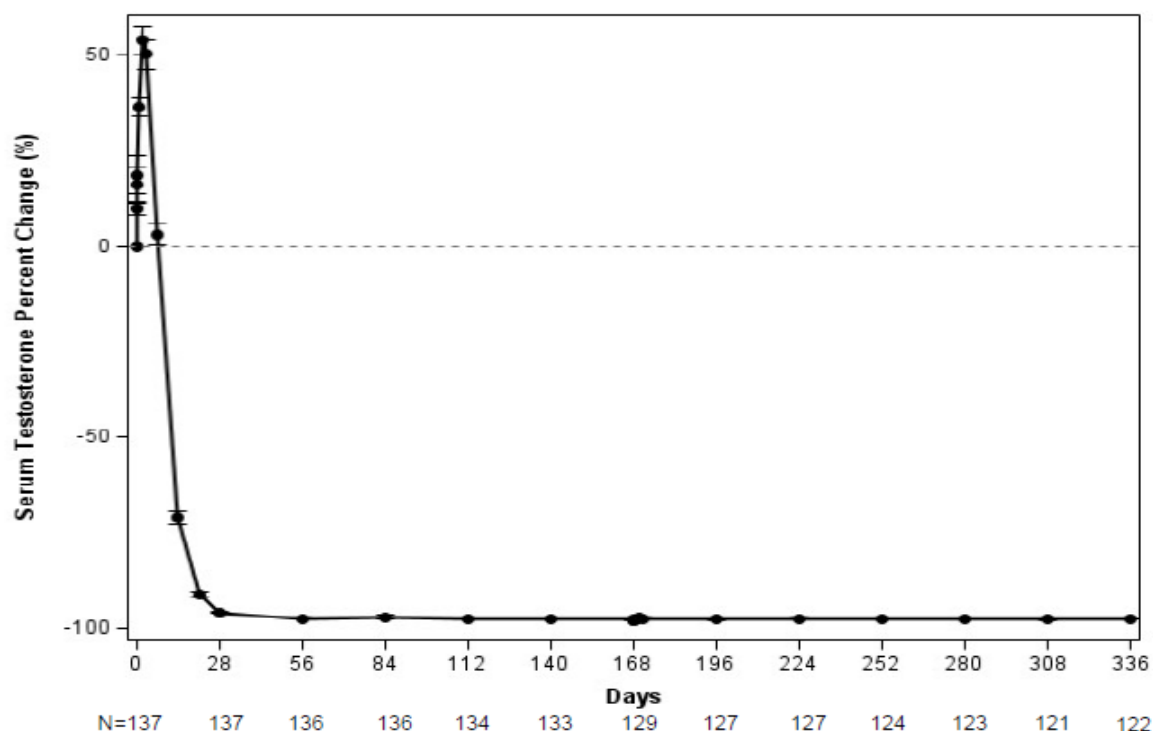
FP01C-13-001 (CAMCEVI 42 mg for 6-Month Administration):

The efficacy of CAMCEVI was evaluated in an open label, single arm, multinational study FP01C-13-001 (NCT02234115) in patients with advanced prostate carcinoma who have a baseline morning serum testosterone level >150 ng/dL and Eastern Cooperative Oncology Group performance status ≤ 2. CAMCEVI was administered subcutaneously at a dose of 42 mg initially on Day 0 and on Week 24.

The population (n = 137) had a median age of 71 years (range 51 to 88) and was 90% White, 6% Black, and 4% Asian. Disease stage was distributed as follows: 23% metastatic (M1), 27% locally advanced (T3/4 NX M0 or any T N1 M0), 26% localized (T1 or T2 N0 M0), and 24% not classifiable. The median testosterone concentration at baseline was 440 ng/dL.

The major efficacy outcome measure was medical castration rate, defined as achieving and maintaining serum testosterone suppression to ≤ 50 ng/dL by Week 4 through Week 48 of treatment. Following the first injection of CAMCEVI, serum testosterone levels were suppressed to ≤ 50 ng/dL by Week 4 (+/-7 days) in 98.5% of the patients; and from Week 4 through Week 48 in 97.0% of patients (95% CI: 92.2-98.9) estimated using the Kaplan-Meier method. The time course of percent change from baseline in testosterone suppression are shown in Figure 2. The percentage of patients with testosterone suppression to ≤ 20 ng/dL was 69.3% on Day 28.

Figure 2 CAMCEVI Mean (95% CI) Percentage Change from Baseline in Serum Testosterone Concentration Over Time (N =137)



In the clinical trial, PSA levels were monitored and were lowered on average by 51% after 4 weeks after administration of CAMCEVI, 83% after 3 months and remained suppressed throughout the 48 weeks of treatment. These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied. No evidence has shown that the rapidity of PSA decline correlates with clinical benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

CAMCEVI ETM and CAMCEVI are sterile, off-white to pale yellow, viscous, and opalescent injectable emulsions supplied in a kit available as follows:

Product	Strength	Kit Contents	NDC
CAMCEVI ETM	21 mg	- pre-filled syringe containing 21 mg leuprolide - a sterile 18-gauge SurGuard®3 safety needle - Prescribing Information.	69448-024-63
CAMCEVI	42 mg	- pre-filled syringe containing 42 mg leuprolide - a sterile 18-gauge SurGuard®3 safety needle - Prescribing Information.	69448-023-63

Store at 2 °C to 8 °C (36 °F to 46 °F). Protect from light by storing in the original package until time of use. Do not freeze or shake.

Excursions permitted to room temperature 25 °C (77 °F) for up to 6 days.

The rubber used in syringe tip cap and plunger stopper is not made of natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity

- Inform patients that CAMCEVI ETM and CAMCEVI are contraindicated in patients who have experienced hypersensitivity with other GnRH agonist drugs, including CAMCEVI ETM and CAMCEVI [see *Contraindications* (4)].

Tumor Flare

- Inform patients that CAMCEVI ETM and CAMCEVI can cause tumor flare during the first weeks of treatment. Inform patients that the increase in testosterone can cause an increase in urinary symptoms or pain. Advise patients to contact their healthcare provider if ureteral obstruction, spinal cord compression, paralysis, or new or worsened symptoms occur after beginning CAMCEVI ETM or CAMCEVI treatment [see *Warnings and Precautions* (5.1)].

Hyperglycemia and Diabetes

- Advise patients that there is an increased risk of hyperglycemia and diabetes with CAMCEVI ETM and CAMCEVI treatment. Inform patients that periodic monitoring for hyperglycemia and diabetes is required when being treated with CAMCEVI ETM or CAMCEVI [see *Warnings and Precautions* (5.2)].

Cardiovascular Diseases

- Inform patients that there is an increased risk of myocardial infarction, sudden cardiac death, and stroke with CAMCEVI ETM and CAMCEVI treatment. Advise patients to immediately report signs and symptoms associated with these events to their healthcare provider for evaluation [see *Warnings and Precautions* (5.3)].

QT/QTc Prolongation

- Inform patients that CAMCEVI ETM and CAMCEVI can cause QT/QTc prolongation. Advise patients to immediately contact their healthcare provider in the event of syncope, presyncopal symptoms, or cardiac palpitations [see *Warnings and Precautions* (5.4)].

Convulsions

- Inform patients that there is an increased risk of convulsions with CAMCEVI ETM and CAMCEVI treatment. Advise patients to immediately contact their healthcare provider if they experience convulsions [see *Warnings and Precautions* (5.5)].

Severe Cutaneous Adverse Reactions

- Inform patients that severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), which may be life threatening or fatal, may occur during treatment with CAMCEVI ETM and CAMCEVI. Advise patients to contact their healthcare provider or seek medical attention right away if they experience signs or symptoms of SCARs, e.g., a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy [see *Warnings and Precautions* (5.6)].

Injection Site Reactions

- Inform patients that injection site related adverse reactions may occur such as transient burning/stinging, pain, bruising, and redness. Advise patients to contact their healthcare provider if they experience rash or severe injection site reactions [see *Adverse Reactions* (6.1)].

Urogenital Disorders

- Advise patients that CAMCEVI ETM and CAMCEVI may cause impotence.

Infertility

- Inform patients that CAMCEVI ETM and CAMCEVI may cause infertility [see *Use in Specific Populations* (8.3)].



Manufactured for:
Accord BioPharma, Inc.
8041 Arco Corporate Drive, Suite 200
Raleigh, NC 27617, USA

By:
Fareva Pau
Fareva Pau, Avenue du Bearn, IDRON, 64320, France