

# CAVERJECT™ Sterile Powder

Alprostadil

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## Presentations

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CAVERJECT is a white crystalline powder containing 10 µg or 20 µg alprostadil in a 5 ml clear glass vial.

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## Uses

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### Actions

Alprostadil is the naturally occurring form of prostaglandin E<sub>1</sub> (PGE<sub>1</sub>). Alprostadil has a wide variety of pharmacological actions; vasodilation and inhibition of platelet aggregation are among the most notable of these effects. In most animal species tested, alprostadil relaxed retractor penis and corpus cavernosum urethrae in vitro. Alprostadil also relaxed isolated preparations of human corpus cavernosum and spongiosum, as well as cavernous arterial segments contracted by either noradrenaline or PGF<sub>2α</sub> in vitro. In pigtail monkeys (*Macaca nemestrina*), alprostadil increased cavernous arterial blood flow in vivo. The degree and duration of cavernous smooth muscle relaxation in this animal model was dose-dependent.

Alprostadil induces erection by relaxation of trabecular smooth muscle and by dilation of cavernosal arteries. This leads to expansion of lacunar spaces and entrapment of blood by compressing the venules against the tunica albuginea, a process referred to as the corporal veno-occlusive mechanism.

### Pharmacokinetics

*Absorption:* For the treatment of erectile dysfunction, alprostadil is administered by injection into the corpora cavernosa. The absolute bioavailability of alprostadil has not been determined.

*Distribution:* Following intracavernosal injection of 20 micrograms alprostadil, mean peripheral plasma concentrations of alprostadil at 30 and 60 minutes after injection (89 and 102 picograms/milliliter, respectively) were not significantly greater than baseline levels of endogenous alprostadil (96 picograms/milliliter). Alprostadil is bound in plasma primarily to albumin (81% bound) and to a lesser extent α-globulin IV-4 fraction (55% bound). No significant binding to erythrocytes or white blood cells was observed.

*Metabolism:* Alprostadil is rapidly converted to compounds which are further metabolized prior to excretion. Following intravenous administration, approximately 80% of circulating alprostadil is metabolized in one pass through the lungs, primarily by beta- and omega-oxidation. Hence, any alprostadil entering the systemic circulation following intracavernosal injection is very rapidly metabolized. The primary metabolites of alprostadil are 15-keto-PGE<sub>1</sub>, 15-keto-13,14-dihydro-PGE<sub>1</sub>, and 13,14-dihydro-PGE<sub>1</sub>. In contrast to 15-keto-PGE<sub>1</sub> and 15-keto-13,14-dihydro-PGE<sub>1</sub>, which lack almost completely biological activity, 13,14-dihydro-PGE<sub>1</sub> has been shown to lower blood pressure and inhibit platelet aggregation.

Following intravenous or intraarterial administration of alprostadil, levels of this metabolite were in the same order of magnitude as those of PGE<sub>1</sub>, while levels of 15-keto-13,14-dihydro-PGE<sub>1</sub>, the major circulating metabolite, were more than 10-fold higher. Plasma 15-keto-PGE<sub>1</sub> remained undetectable throughout the observation period. Following intracavernosal injection of 20 micrograms alprostadil, peripheral levels of the major circulating metabolite, 13,14-dihydro-15-oxo-PGE<sub>1</sub>, increased to reach a peak 30 minutes after injection and returned to pre-dose levels by 60 minutes after injection while peripheral levels of alprostadil were not significantly greater than baseline levels. Plasma concentrations of 13,14-dihydro-PGE<sub>1</sub> were not determined.

*Elimination:* The metabolites of alprostadil are excreted primarily by the kidney, with almost 90% of an administered intravenous dose excreted in urine within 24 hours post-dose. The remainder of the dose is excreted in the feces. There is no evidence of tissue retention of alprostadil or its metabolites following intravenous administration. In healthy men, 70% to 90% of alprostadil is extensively extracted and metabolized in a single pass through the lungs, resulting in a metabolic half-life of less than one minute.

### **Pharmacokinetics in Subpopulations:**

**Effects of Age or Race:** The potential effect of age or race on the pharmacokinetics of alprostadil following intracavernous use has not been evaluated.

*Effect of Renal or Hepatic Impairment:* Pulmonary first-pass metabolism is the primary factor influencing the systemic clearance of alprostadil. Although the pharmacokinetics of alprostadil have not been formally examined in patients with renal or hepatic insufficiency, alterations in renal or hepatic function would not be expected to have a major influence on the pharmacokinetics of alprostadil

### **Indications**

CAVERJECT is indicated for the treatment of erectile dysfunction.

CAVERJECT may be a useful adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

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## **Dosage & Administration**

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*General Information:* CAVERJECT is administered by direct intracavernosal injection. A 1/2-inch, 27- to 30-gauge needle is recommended. The dose of CAVERJECT should be individualized by careful titration under a physician's supervision.

The first injections of CAVERJECT must be done at the physician's office by medically trained personnel. Self-injection therapy by the patient can be started only after the patient is properly instructed and well trained in the self-injection technique. The physician should make a careful assessment of the patient's skills and competence with this procedure. The intracavernosal injection must be done under sterile conditions. The site of injection is usually along either dorso-lateral aspect of the proximal third of the penis. Visible veins should be avoided. Alternate which side of the penis is injected and vary the site of injection

Reconstituted solutions of CAVERJECT are intended for single use only; discard after use. Instruct the user in the proper disposal of the syringe, needle, and vial or ampoule.

*Initial Titration in Physician's Office:* During dose titration, the patient must stay in the physician's office until complete detumescence occurs. If there is no response, the next higher dose may be given within one hour. If there is a response, allow at least a one-day interval before administering the next dose.

*Erectile Dysfunction of Vasculogenic, Psychogenic, or Mixed Etiology.* Dosage titration should be initiated at 2.5 micrograms of alprostadil. If there is a partial response, the dose may be increased by 2.5 micrograms to a dose of 5 micrograms and then in increments of 5 to 10 micrograms, depending upon erectile response, until the dose that produces an erection suitable for intercourse and not exceeding a duration of one hour is reached. If there is no response to the initial 2.5 microgram dose, the second dose may be increased to 7.5 micrograms, followed by increments of 5 to 10 micrograms.

*Erectile Dysfunction of Pure Neurogenic Etiology (Spinal Cord Injury).* Dosage titration should be initiated at 1.25 micrograms of alprostadil. The dose may be increased by 1.25 micrograms to a dose of 2.5 micrograms, followed by an increment of 2.5 micrograms to a dose of 5 micrograms, and then in 5 microgram increments until the dose that produces an erection suitable for intercourse and not exceeding a duration of one hour is reached.

*Maintenance Therapy: Self-Injection:* The dose of CAVERJECT that is selected for self-injection treatment should provide the patient with an erection that is satisfactory for sexual intercourse and that is maintained for no longer than one hour. If the duration of erection is longer than one hour, the dose of CAVERJECT should be reduced. Self-injection therapy for use at home should be initiated at the dose that was determined in the physician's office; however, if dose adjustment is required, it should be done only after consultation with the physician. The dose should be adjusted in accordance with the titration guidelines described above. The lowest effective dose should be employed. The recommended frequency of injection is no more than three times weekly with at least 24 hours between each dose. The patient may expect an erection to develop within 5 to 20 minutes.

The effectiveness of CAVERJECT for long-term use of up to six months has been documented in an uncontrolled, self-injection study. The mean dose of alprostadil at the end of six months was 20.7 micrograms. In the majority of patients, the maintenance dose is between 5 micrograms and 20 micrograms. Maintenance doses of greater than 60 micrograms are not recommended.

*CAVERJECT as an Adjunct to the Diagnosis of Erectile Dysfunction:* In the simplest diagnostic test for erectile dysfunction (pharmacologic testing), patients are monitored for the occurrence of an erection after an intracavernosal injection of CAVERJECT. Extensions of this testing include the use of CAVERJECT as an adjunct to laboratory investigations, such as duplex or Doppler imaging, <sup>133</sup>Xenon washout tests, radioisotope penogram, and penile arteriography, to allow visualization and assessment of penile vasculature. For any of these tests, a single dose of CAVERJECT that induces an erection with firm rigidity should be used.

*Treatment Monitoring Recommendations:* Regular follow-up is indicated while the patient is in the self-injection program. This is especially true for the initial self-injections, since adjustments in the dose of CAVERJECT may be needed.

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## Contraindications

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CAVERJECT is contraindicated in the following patients:

- patients who have a known hypersensitivity to the drug
- patients who have conditions that might predispose them to priapism, such as sickle cell anemia or trait, multiple myeloma, or leukemia
- patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease
- patients with penile implants
- patients for whom sexual activity is inadvisable or contraindicated

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## Warnings & Precautions

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Underlying treatable medical causes of erectile dysfunction should be diagnosed and treated prior to initiation of therapy with CAVERJECT.

Priapism (erection lasting over six hours) may occur following intracavernosal administration of CAVERJECT. To minimize the risk select the lowest effective dose and instruct patients to immediately consult with their physician and seek medical assistance for any prolonged erection lasting more than 4 hours. Treatment of priapism should be according to established medical practice.

Penile fibrosis, including angulation, fibrotic nodules, and Peyronie's disease, may occur following the intracavernosal administration of CAVERJECT. The occurrence of fibrosis may increase with increased duration of use of CAVERJECT. Regularly scheduled follow-up and examination of the penis to detect signs of penile fibrosis or Peyronie's disease is strongly recommended. Treatment with CAVERJECT should be discontinued in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease.

Because a small amount of bleeding may occur at the injection site patients should be counseled about the protective measures that are necessary to guard against the spread of sexually transmitted diseases, including HIV, and blood-borne diseases. Patients on anticoagulants, such as warfarin or heparin, may have increased propensity for bleeding after intracavernosal injection.

*Pregnancy & Lactation:* Not Applicable

*Effects on Ability to Drive & Use Machines:* None known.

*Carcinogenicity/Mutagenicity:* Long-term carcinogenicity studies have not been conducted. The following battery of mutagenicity assays revealed no potential for mutagenesis: bacterial mutation (Ames), alkaline elution, rat micronucleus, sister chromatid exchange, CHO/HGPRT mammalian cell forward gene mutation, and unscheduled DNA synthesis (UDS).

*Impairment of Fertility/Effect on Reproduction:* Rat reproductive studies indicate that alprostadil at doses of up to 2.0 milligram/kilogram/day (s.c.) does not adversely affect or alter rat spermatogenesis.

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## Adverse Effects

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The most frequent adverse reaction after intracavernosal injection of CAVERJECT is mild to moderate penile pain reported in approximately 11% of self-injections by men in clinical studies. It was reported at least once by about one third of all patients, although only 3% discontinued use for this reason. Penile fibrosis, including angulation, fibrotic nodules, and Peyronie's disease, was reported in 3% of clinical trial patients overall, however, in one self-injection study in which the duration of use was up to 18 months, the incidence of penile fibrosis was approximately 8% (see Warnings and Precautions).

Hematoma and ecchymosis at the site of injection, which are related to the injection technique rather than to the effects of CAVERJECT, occurred in 3% and 2% of patients, respectively. Prolonged erection (defined as an erection that lasts for four to six hours) after intracavernosal administration of CAVERJECT was reported in 4% of patients. The frequency of priapism (defined as an erection that lasts six hours or longer) was 0.4% (see Warnings and Precautions). In the majority of cases, spontaneous detumescence occurred.

The following local adverse reactions were reported by fewer than 1% of patients in clinical studies after intracavernosal injection of CAVERJECT: balanitis, injection site hemorrhage, injection site inflammation, injection site itching, injection site swelling, injection site edema, urethral bleeding, penile warmth, numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, erythema, venous leak, painful erection, and abnormal ejaculation.

The following systemic events, which were judged by the investigator to be possibly related to the use of CAVERJECT, were reported for less than 1% of patients in clinical studies: testicular pain, scrotal disorder (redness, pain, spermatocele), scrotal edema, hematuria, testicular disorder (warmth, swelling, mass, thickening) impaired urination, urinary frequency, urinary urgency, pelvic pain, hypotension, vasodilatation, peripheral vascular disorder, supraventricular extrasystole, vasovagal reactions, hypesthesia, non-generalized weakness, diaphoresis, rash, non-application site pruritus, nausea, dry mouth, increased serum creatinine, leg cramps, and mydriasis.

Hemodynamic changes, manifested as decreases in blood pressure at doses greater than 20 micrograms and increases in pulse rate at doses greater than 30 micrograms, were observed during clinical studies and appeared to be dose-dependent. However these changes were usually clinically unimportant; only three patients discontinued the treatment because of symptomatic hypotension.

CAVERJECT had no clinically important effect on serum or urine laboratory tests.

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## Interactions

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The potential for pharmacokinetic drug-drug interactions between CAVERJECT and other agents has not been formally studied. In clinical trials, concomitant use of agents such as antihypertensive drugs, diuretics, antidiabetic agents (including insulin), or non-steroidal anti-inflammatory drugs had no effect on the safety or efficacy of CAVERJECT. The safety and efficacy of combinations of CAVERJECT and other vasoactive agents have not been systematically studied.

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## Overdosage

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Overdosage was not observed in clinical trials with CAVERJECT. If intracavernous overdose of CAVERJECT occurs, the patient should be placed under medical supervision until any systemic effects have resolved and/or until penile detumescence has occurred. Symptomatic treatment of any systemic symptoms would be appropriate.

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## Pharmaceutical Precautions

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*Stability/Shelf life & Special Precautions for Storage:* CAVERJECT sterile powder should be stored at or below 25°C. The reconstituted solution should be used immediately. Reconstituted solutions of alprostadil sterile powder should not be frozen.

*Incompatibilities:* Only the accompanying bacteriostatic water for injection should be used when reconstituting CAVERJECT sterile powder.

*Instructions for use/handling:* Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit.

Bacteriostatic Water for Injection or sterile water, both preserved with benzyl alcohol 0.945% w/v, must be used as the diluent for reconstitution of CAVERJECT sterile powder. After reconstitution with 1 milliliter of diluent, the volume of the resulting solution is 1.13 milliliters. One milliliter of this solution will contain either 10.5 or 20.5 micrograms of alprostadil depending on vial strength. The deliverable amount of alprostadil is 10 or 20 micrograms per milliliter because approximately 0.5 microgram is lost due to adsorption to the vial and syringe.

*List of Excipients:* CAVERJECT Sterile Powder: Lactose (diluent), sodium citrate (pH buffer), hydrochloric acid solution 10% (adjust pH), sodium hydroxide solution (adjust pH), benzyl alcohol (preservative), water for injection (solvent).

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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CAVERJECT sterile powder is supplied in 5-millilitre glass vials with 1 ml prefilled diluent syringes in packs of 1's.

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## Further Information

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Alprostadil is a white to off-white crystalline powder with a melting point between 115°C-116°C. Its solubility at 35°C is 8000 micrograms per 100 milliliter double distilled water. The acid dissociation constant (Ka) is approximately  $1.1 \times 10^{-5}$ . The chemical name is (11a,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid. Molecular weight is 354.49.

CAVERJECT Sterile Powder is available in the following strengths:

Strength (mcg)	Alprostadil concentration when reconstituted as directed (mcg/mL)	Total alprostadil content/vial (mcg)
10	10	11.9
20	20	23.2

A 1-year irritancy study was conducted in Cynomolgus monkeys injected intracavernosally twice weekly with either vehicle or 3 or 8.25 micrograms of alprostadil per injection. Additional monkeys were injected as described previously plus they received multiple doses during weeks 44, 48, and 52. Monkeys from each group were retained for a 4-week recovery period. There was no evidence of drug-related penile irritancy or nonpenile tissue lesions, which could be directly related to alprostadil. The irritancy which was noted for control and treated monkeys was considered to be a result of the injection procedure itself, and any lesions noted were shown to be reversible. At the end of the 4-week recovery period, the histological changes in the penis had regressed.

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## Name & Address

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