

Caverject®

(alprostadil injection)
aqueous



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&Upjohn

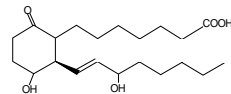
For Intracavernosal Use

DESCRIPTION

CAVERJECT injection contains alprostadil as the naturally occurring form of prostaglandin E₁ (PGE₁) and is designated chemically as (11 α ,13E,15E)-11,15-dihydroxy-9-oxoprost-13-en-1- α -ic acid. The molecular weight is 354.49.

Alprostadil is a white to off-white crystalline powder with a melting point between 115° and 116°C. Its solubility at 35°C is 8000 micrograms (mcg) per 100 milliliter double distilled water. CAVERJECT injection is available as a sterile isotonic solution in one milliliter ampoules containing 10.2 or 20.2 mcg per mL of alprostadil, depending on ampoule strength. The deliverable amount of alprostadil is 10 or 20 mcg/mL because approximately 0.2 mcg is lost due to adsorption to the syringe during administration. CAVERJECT injection is also available in two milliliter ampoules containing 40.4 mcg/2 mL (20.2 mcg/mL) of alprostadil. The deliverable amount of alprostadil is 40 mcg/2 mL (20 mcg/mL) because approximately 0.4 mcg is lost due to adsorption to the syringe during administration. Each mL also contains 8.2 mg sodium chloride, 1.5 mg sodium citrate, a trace of dehydrated alcohol, and water for injection. When necessary, the pH of alprostadil aqueous injection was adjusted with hydrochloric acid and/or sodium hydroxide before filling.

The structural formula of alprostadil is represented below:



CLINICAL PHARMACOLOGY

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_{2 α} . *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 mcg alprostadil, mean peripheral plasma concentrations of alprostadil at 30 and 60 minutes after injection (89 and 102 picograms/mL, respectively) were not significantly greater than baseline levels of endogenous alprostadil (96 picograms/mL). Plasma levels of alprostadil were measured using a radioimmunoassay method. 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. Following intracavernosal injection of 20 mcg

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alprostadil, peripheral levels of the major circulating metabolite, 13,14-dihydro-15-oxo-PGE₁, increased to reach a peak 30 minutes after injection and returned to pre-dose levels by 60 minutes after injection.

Excretion: The metabolites of alprostadil are excreted primarily by the kidney, with almost 30% 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.

Pharmacokinetics in Special Populations

Geriatric: The potential effect of age on the pharmacokinetics of alprostadil has not been formally evaluated. In patients with acute respiratory distress syndrome (ARDS), the mean (\pm SD) pulmonary extraction of alprostadil was 72% \pm 15% in 11 elderly patients aged 65 years or older (mean, 71 \pm 6 years) and 65% \pm 20% in 6 young patients aged 35 years or younger (mean, 28 \pm 5 years).

Pediatric: Alprostadil plasma concentrations were measured in 10 neonates (gestational age of 34 weeks in 2 infants and 38 to 40 weeks in 8 infants) receiving steady-state intravenous infusions of alprostadil to treat underlying cardiac malformations. Infusion rates of alprostadil ranged from 5 to 50 (median, 45) nanograms/kilogram/minute, resulting in alprostadil plasma concentrations ranging between 22 and 530 (median, 56) picograms/mL. The wide range of alprostadil plasma concentrations in neonates reflects high variability in individual clearances of alprostadil in this patient population.

Gender: The potential influence of gender on the pharmacokinetics of alprostadil has not been formally studied in healthy subjects. Two studies determined the pulmonary extraction of alprostadil following intravascular administration in 23 patients with ARDS. The mean (\pm SD) pulmonary extraction was 66% \pm 20% in 17 male patients and 69% \pm 18% in 6 female patients, suggesting that the pharmacokinetics of alprostadil are not influenced by gender.

Race: The potential influence of race in the pharmacokinetics of alprostadil has not been formally evaluated.

Renal and Hepatic Insufficiency: Pulmonary first-pass metabolism is the primary factor influencing the systemic clearance of alprostadil. The pharmacokinetics of alprostadil have not been formally studied in patients with renal or hepatic insufficiency.

Pulmonary Disease: The pulmonary extraction of alprostadil following intravascular administration was reduced by 15% (66 \pm 3.2% vs 78 \pm 2.4%) in patients with ARDS compared with a control group of patients with normal respiratory function who were undergoing cardiopulmonary bypass surgery. Pulmonary clearance was found to vary as a function of cardiac output and pulmonary intrinsic clearance in a group of 14 patients with ARDS or at risk of developing ARDS following trauma or sepsis. In this study, the extraction efficiency of alprostadil ranged from subnormal (11%) to normal (90%), with an overall mean of 67%.

Drug-Drug Interactions: The potential for pharmacokinetic drug-drug interactions between alprostadil and other agents has not been formally studied.

INDICATION AND USAGE

CAVERJECT injection is indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

Intracavernosal CAVERJECT is also indicated as an adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

CONTRAINDICATIONS

CAVERJECT injection should not be used in patients who have a known hypersensitivity to the drug, in patients who have conditions that might predispose them to priapism, such as sickle cell anemia or trait, multiple myeloma, or leukemia, or in patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease. Patients with penile implants should not be treated with CAVERJECT.

CAVERJECT is intended for use in adult men only. CAVERJECT is not indicated for use in children or newborns.

CAVERJECT should not be used in men for whom sexual activity is inadvisable or contraindicated.

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WARNINGS

Prolonged erection defined as erection lasting > 4 to \leq 6 hours in duration occurred in 4% of 1861 patients treated up to 18 months in studies of CAVERJECT Sterile Powder. The incidence of priapism (erections lasting > 6 hours in duration) was 0.4% with the same length of use. Pharmacologic intervention and/or aspiration of blood from the corpora cavernosum was performed in 2 of the 7 patients with priapism. To minimize the chances of prolonged erection or priapism, CAVERJECT injection should be titrated slowly to the lowest effective dose (see DOSAGE AND ADMINISTRATION). The patient must be instructed to immediately report to his prescribing physician, or, if unavailable, to seek immediate medical assistance for any erection that persists longer than 4 hours. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

PRECAUTIONS

General Precautions

- The overall incidence of penile fibrosis, including Peyronie's disease, reported in clinical studies with CAVERJECT Sterile Powder was 3%. In one self-injection clinical study where duration of use was up to 18 months, the incidence of fibrosis was 7.8%. Regular follow-up of patients, with careful examination of the penis, is strongly recommended to detect signs of penile fibrosis. Treatment with CAVERJECT should be discontinued in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease.
- Intracavernosal injections of CAVERJECT can lead to increased peripheral blood levels of PGE₁ and its metabolites, especially in those patients with significant corpora cavernosa venous leakage. Increased peripheral blood levels of PGE₁ and its metabolites may lead to hypotension and/or dizziness.
- Patients on anticoagulants, such as warfarin or heparin, may have increased propensity for bleeding after intracavernosal injection.
- Underlying treatable medical causes of erectile dysfunction should be diagnosed and treated prior to initiation of therapy with CAVERJECT.
- The safety and efficacy of combinations of CAVERJECT and other vasoactive agents have not been systematically studied. Therefore, the use of such combinations is not recommended.
- The patient should be instructed not to re-use or to share needles or syringes. As with all prescription medicines, the patient should not allow anyone else to use his medicine.

Information for the Patient:

The patient should be instructed to transfer the solution from the pharmacy to his home freezer or refrigerator as soon as possible. Brief (2 hours or less) exposure to conditions as warm as 25°C (77°F) will not harm the product.

To ensure safe and effective use of CAVERJECT, the patient should be thoroughly instructed and trained in the self-injection technique before he begins intracavernosal treatment with CAVERJECT at home. The desirable dose should be established in the physician's office.

Any ampoule containing sterile solution with precipitates or discoloration should be discarded. The ampoule is designed for one use only and should be discarded after withdrawal of proper volume of the solution. Needles must be properly discarded after use; they must not be re-used or shared with other persons. Patient instructions for administration are included in each package of CAVERJECT.

The dose of CAVERJECT that is established in the physician's office should not be changed by the patient without consulting the physician. The patient may expect an erection to occur within 5 to 20 minutes. A standard treatment goal is to produce an erection lasting no longer than 1 hour. Generally, CAVERJECT should be used no more than 3 times per week, with at least 24 hours between each use.

Patients should be aware of possible side effects of therapy with CAVERJECT, the most frequently occurring is penile pain after injection, usually mild to moderate in severity. A potentially serious adverse reaction with intracavernosal therapy is priapism. Accordingly, the patient should be instructed to contact the physician's office immediately or, if unavailable, to seek immediate medical assistance if an erection persists for longer than 4 hours.

The patient should report any penile pain that was not present before or that increased in intensity, as well as

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the occurrence of nodules or hard tissue in the penis to his physician as soon as possible. As with any injection, an infection is a possibility. Patients should be instructed to report to the physician any penile redness, swelling, tenderness or curvature of the erect penis. The patient must visit the physician's office for regular checkups for assessment of the therapeutic benefit and safety of treatment with CAVERJECT.

Note: Use of intracavernosal CAVERJECT offers no protection from the transmission of sexually transmitted diseases. Individuals who use CAVERJECT should be counseled about the protective measures that are necessary to guard against the spread of sexually transmitted diseases, including the human immunodeficiency virus (HIV).

The injection of CAVERJECT can induce a small amount of bleeding at the site of injection (see ADVERSE REACTIONS section-hematoma, ecchymosis, hemorrhage at the site of injection). In patients infected with blood-borne diseases, this could increase the risk of transmission of blood-borne diseases between partners.

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 efficacy or safety of CAVERJECT.

Carcinogenesis, Mutagenesis, and

Impairment of Fertility:

Long-term carcinogenicity studies have not been conducted. Rat reproductive studies indicate that alprostadil at doses of up to 0.2 mg/kg/day does not adversely affect or alter rat spermatogenesis, providing a 200-fold margin of safety compared with the usual human doses. 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).

A 1-year iritancy study was conducted in three groups of 5 male Cynomolgus monkeys injected intracavernosally twice weekly with either vehicle or 3 or 8.25 mcg of alprostadil/injection. An additional two groups of 6 monkeys each were injected with vehicle or with 8.25 mcg/injection twice weekly as described previously plus they received multiple doses during weeks 44, 48, and 52. Three monkeys from each group were retained for a 4-week recovery period. There was no evidence of drug-related penile iritancy or nonpenile tissue lesions, which could be directly related to alprostadil. The iritancy 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.

Pregnancy, Nursing Mothers, and Pediatric Use:

CAVERJECT is not indicated for use in pediatric patients or women.

ADVERSE REACTIONS

Local Adverse Reactions: The following local adverse reaction information was derived from controlled and uncontrolled studies of CAVERJECT Sterile Powder, including an uncontrolled 18-month safety study.

Local Adverse Reactions Reported by \geq 1% of Patients Treated with CAVERJECT Sterile Powder for up to 18 Months*

Event	CAVERJECT N = 1861
Penile pain	37%
Prolonged erection	4%
Penile fibrosis**	3%
Injection site hematoma	3%
Penis disorder***	3%
Injection site ecchymosis	2%
Penile rash	1%
Penile edema	1%

* Except for penile pain (2%), no significant local adverse reactions were reported by 294 patients who received 1 to 3 injections of placebo.

** See General Precautions.

*** Includes numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, erythema, venous leak, penile skin tear, strange feeling of penis, discoloration of penile head, itch at tip of penis.

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Penile Pain: Penile pain after intracavernosal administration of CAVERJECT was reported at least once by 37% of patients in clinical studies of up to 18 months in duration. In the majority of the cases, penile pain was rated mild or moderate in intensity. Three percent of patients discontinued treatment because of penile pain. The frequency of penile pain was 2% in 294 patients who received 1 to 3 injections of placebo.

Prolonged Erection/Priapism: In clinical trials, prolonged erection was defined as an erection that lasted for 4 to 6 hours; priapism was defined as an erection that lasted 6 hours or longer. The frequency of prolonged erection after intracavernosal administration of CAVERJECT was 4%, while the frequency of priapism was 0.4% (see WARNINGS).

Hematoma/Ecchymosis: The frequency of hematoma and ecchymosis was 3% and 2%, respectively. In most cases, hematoma/ecchymosis was judged to be a complication of a faulty injection technique. Accordingly, proper instruction of the patient in self-injection is of importance to minimize the potential of hematoma/ecchymosis (see DOSAGE AND ADMINISTRATION).

The following local adverse reactions were reported by fewer than 1% of patients after 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.

Systemic Adverse Events: The following systemic adverse event information was derived from controlled and uncontrolled studies of CAVERJECT Sterile Powder, including an uncontrolled 18-month safety study.

Systemic Adverse Events Reported by ≥ 1% of Patients Treated with CAVERJECT Sterile Powder for up to 18 Months*

Body System/Reaction	CAVERJECT N = 1861
Cardiovascular System	
Hypertension	2%
Central Nervous System	
Headache	2%
Dizziness	1%
Musculoskeletal System	
Back pain	1%
Respiratory System	
Upper respiratory infection	4%
Flu syndrome	2%
Sinusitis	2%
Nasal congestion	1%
Cough	1%
Urogenital System	
Prostatic Disorder**	2%
Miscellaneous	
Localized pain***	2%
Trauma****	2%

* No significant adverse events were reported by 294 patients who received 1 to 3 injections of placebo.

** prostatitis, pain, hypertrophy, enlargement

*** pain in various anatomical structures other than injection site

**** injuries, fractures, abrasions, lacerations, dislocations

The following systemic events, which were reported for < 1% of patients in clinical studies, were judged by investigators to be possibly related to use of CAVERJECT: testicular pain, scrotal disorder, scrotal edema, hematuria, testicular disorder, impaired urination, urinary frequency, urinary urgency, pelvic pain, hypotension, vasodilation, peripheral vascular disorder, supraventricular extrasystoles, vasovagal reactions, hypesthesia, non-generalized weakness, diaphoresis, rash, non-application site pruritus, skin neoplasm, nausea, dry mouth, increased serum creatinine, leg cramps, and mydriasis.

Hemodynamic changes, manifested as decreases in blood pressure and increases in pulse rate, were observed during clinical studies, principally at doses above 20 mcg and above 30 mcg of alprostadil, respectively, 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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Needle breakage: During post-marketing surveillance, needle breakage requiring surgical extraction has been reported with the administration of CAVERJECT Sterile Powder. Careful instruction in proper patient handling and injection techniques may minimize the potential of needle breakage.

OVERDOSAGE

Overdosage was not observed in clinical trials with CAVERJECT. If intracavernosal overdose of CAVERJECT occurs, the patient should be 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.

DOSAGE AND ADMINISTRATION

The dose of CAVERJECT should be individualized for each patient by careful titration under supervision by the physician. In clinical studies, patients were treated with CAVERJECT Sterile Powder in doses ranging from 0.2 to 140 mcg; however, since 99% of patients received doses of 60 mcg or less, doses of greater than 60 mcg are not recommended. In general, the lowest possible effective dose should always be employed. In clinical studies, over 80% of patients experienced an erection sufficient for sexual intercourse after intracavernosal injection of CAVERJECT.

A 1/2-inch, 27- to 30-gauge needle is generally recommended.

Initial Titration in Physician's Office:

Erectile Dysfunction of Vasculogenic, Psychogenic, or Mixed Etiology: Dosage titration should be initiated at 2.5 mcg of alprostadil. If there is a partial response, the dose may be increased by 2.5 mcg to a dose of 5 mcg and then in increments of 5 to 10 mcg, depending upon erectile response, until the dose that produces an erection suitable for intercourse and not exceeding a duration of 1 hour is reached. If there is no response to the initial 2.5-mcg dose, the second dose may be increased to 7.5 mcg, followed by increments of 5 to 10 mcg. The patient must stay in the physician's office until complete detumescence occurs. If there is no response, then the next higher dose may be given within 1 hour. If there is a response, then there should be at least a 1-day interval before the next dose is given.

Erectile Dysfunction of Pure Neurogenic Etiology (Spinal Cord Injury): Dosage titration should be initiated at 1.25 mcg of alprostadil. The dose may be increased by 1.25 mcg to a dose of 2.5 mcg, followed by an increment of 2.5 mcg to a dose of 5 mcg, and then in 5-mcg increments until the dose that produces an erection suitable for intercourse and not exceeding a duration of 1 hour is reached. The patient must stay in the physician's office until complete detumescence occurs. If there is no response, then the next higher dose may be given within 1 hour. If there is a response, then there should be at least a 1-day interval before the next dose is given.

The majority of patients (56%) in one clinical study involving 579 patients were titrated to doses of greater than 5 mcg but less than or equal to 20 mcg. The mean dose at the end of the titration phase was 17.8 mcg of alprostadil.

Maintenance Therapy:

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 determine the most suitable size needle for the patient and instruct the patient on the appropriate size to use for self-injection. Two needles are provided in the Companion Pack; a 1/2-inch, 27 gauge needle and a 1/2-inch, 30 gauge needle. 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 the dorso-lateral aspect of the proximal third of the penis. Visible veins should be avoided. The side of the penis that is injected and the site of injection must be alternated; the injection site must be cleansed with an alcohol swab.

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 1 hour. If the duration of erection is longer than 1 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

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the physician's office; however, dose adjustment, if required, may be made only after consultation with the physician. The dose should be adjusted in accordance with the titration guidelines described above. The effectiveness of CAVERJECT for long-term use of up to 6 months has been documented in an uncontrolled, self-injection study. The mean dose of CAVERJECT Sterile Powder at the end of 6 months was 20.7 mcg in this study.

Careful and continuous follow-up of the patient while in the self-injection program must be exercised. This is especially true for the initial self-injections, since adjustments in the dose of CAVERJECT may be needed. The recommended frequency of injection is no more than 3 times weekly, with at least 24 hours between each dose. The ampoule of CAVERJECT is intended for single use only and should be discarded after use. The user should be instructed in the proper disposal of the syringe, needle, and ampoule.

While on self-injection treatment, it is recommended that the patient visit the prescribing physician's office every 3 months. At that time, the efficacy and safety of the therapy should be assessed, and the dose of CAVERJECT should be adjusted, if needed.

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 are the use of CAVERJECT as an adjunct to laboratory investigations, such as duplex or Doppler imaging, ¹²⁵I Xenon washout tests, radiolabeled 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.

General Procedure for Dose Preparation:

CAVERJECT Injection is packaged in a one milliliter polyethylene ampoule containing 10.2 or 20.2 mcg per mL of alprostadil, depending on ampoule strength. The deliverable amount of alprostadil is 10 or 20 mcg/mL because approximately 0.2 mcg is lost due to adsorption to the syringe during administration. CAVERJECT Injection is also available in two milliliter ampoules containing 40.4 mcg/2 mL (20.2 mcg/mL) of alprostadil. The deliverable amount of alprostadil is 40 mcg/2 mL (20 mcg/mL) because approximately 0.4 mcg is lost due to adsorption to the syringe during administration. To prepare a dose for administration, remove the ampoule from the foil wrapping. Allow the ampoule contents to warm to room temperature. The ampoule should not be cool to the touch. Do not immerse in water. Do not microwave.

Shake the ampoule vigorously for at least 30 seconds. Next, hold the shorter tab closest to the neck of the ampoule and shake it downward with a quick snap to clear any solution from the neck. Holding the ampoule by the edges, twist the top of the ampoule and lift upward to remove it. Make sure the open end of the ampoule does not touch your hands or any other surface. After opening the ampoule, the solution should be immediately transferred to a syringe and used promptly. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit.

Caution: Do not re-use any remaining CAVERJECT solution due to the possibility of bacterial contamination.

HOW SUPPLIED

CAVERJECT Injection is a sterile isotonic solution supplied in one milliliter polyethylene ampoules containing 10.2 or 20.2 mcg per mL of alprostadil, depending on ampoule strength. The deliverable amount of alprostadil is 10 or 20 mcg/mL because approximately 0.2 mcg is lost due to adsorption to the syringe during administration. CAVERJECT Injection is also available in two milliliter ampoules containing 40.4 mcg/2 mL (20.2 mcg/mL) of alprostadil. The deliverable amount of alprostadil is 40 mcg/2 mL (20 mcg/mL) because approximately 0.4 mcg is lost due to adsorption to the syringe during administration. Each ampoule is packaged in foil wrapping.

Store CAVERJECT Injection frozen at -20° to -10°C (-4° to 14°F) until dispensed. After dispensing, store in a freezer at -20° to -10°C (-4° to 14°F) for up to 3 months. During this 3-month period, CAVERJECT Injection may be moved to and kept in a refrigerator at 2° to 8°C (36° to 46°F) for

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up to 7 days. **Once refrigerated, it must be used within 7 days or discarded; it should not be refrozen.** Once removed from the foil wrapping, the solution in the ampoule should be used immediately after allowing it to warm to room temperature or it should be discarded. Open ampoules of CAVERJECT Injection should be used immediately and not stored. CAVERJECT Injection is available in the following packages:

10 mcg/mL	5 - 1 mL ampoules	NDC 0009-7655-02
20 mcg/mL	5 - 1 mL ampoules	NDC 0009-7654-02
40 mcg/2 mL	5 - 2 mL ampoules (20 mcg/mL)	NDC 0009-7650-02

A carton containing five CAVERJECT Companion Packs is also available. Each pack contains the following:

- 1- 2.0 mL Luer-lock Syringe
- 1- Standard Needle 27 gauge x 1/2"
- 1- Standard Needle 30 gauge x 1/2"
- 1- Alcohol Swab

Only

Manufactured by:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
By:
Pharmacia & Upjohn (Perth) Pty Limited
Bentley, WA 6102, Australia

817 587 102

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PAM207C

Tear along perforated line

Tear along perforated line

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IMPOTENCE: CAUSES AND TREATMENTS

There are several causes of impotence, a condition known medically as erectile dysfunction. These include: medications that you may be taking for other conditions, impaired blood circulation in the penis, nerve damage, emotional problems, excessive smoking or alcohol use, use of street drugs, and hormonal imbalances. Often, impotence is due to more than one cause.

Treatments for impotence include: switching medications (if you are taking a medication that causes impotence), administration of hormones, penile injections, use of medical devices that produce an erection, surgical procedures to correct blood flow in the penis, penile implants, and psychological counseling. Your doctor has selected CAVERJECT to treat your impotence. Your doctor can also discuss other available treatments. You should not stop taking any prescription medications, unless told to do so by your doctor.

USE OF CAVERJECT

CAVERJECT is injected into a specific area of the penis and should produce an erection in 5 to 20 minutes. The erection should last for about 1 hour. Generally, you should not use CAVERJECT more than 3 times a week, with at least 24 hours between uses.

Who Should Not Use CAVERJECT?

Men who have conditions that might result in long-lasting erections should not use CAVERJECT. Some of these conditions include: sickle cell anemia or trait, leukemia, and tumor of the bone marrow (multiple myeloma). Men with penile implants, or an abnormally formed penis, or who have been advised not to engage in sexual activity should not use CAVERJECT. CAVERJECT should not be used by women or children.

What are the Risks of Using CAVERJECT?

Erections that last more than 4 hours can cause serious and permanent damage. **Call your doctor or seek professional help immediately if you still have an erection 4 hours after injection.**

The most common side effect of CAVERJECT is mild to moderate pain after injection. About one-third of patients report this effect.

Call your doctor if you notice any redness, lumps, swelling, tenderness, or curving of the erect penis.

A small amount of bleeding at the injection site may occur. Tell your doctor if you have a condition or are taking a medicine that interferes with blood clotting.

NOTE: CAVERJECT offers no protection from the transmission of sexually transmitted diseases such as HIV (the virus that causes AIDS). Small amounts of bleeding at the injection site can increase the risk of transmission of blood-borne diseases between partners.

There is no approved injectable treatment using multiple drug components or "cocktails" for erectile dysfunction. Moreover, there are no data on the efficacy and safety of these combinations.

STORAGE

- CAVERJECT Injection is distributed and stored in the pharmacy as a frozen pack, which you should place in your freezer or refrigerator as soon as possible. Brief (2 hours or less) exposure to conditions as warm as 25°C (77°F) will not harm your medicine. If placed in your refrigerator, it must be used within 7 days (see #2 below).
- Store unused packs of CAVERJECT Injection in the unopened foil wrapping in your freezer at -20° to -10°C (-4° to 14°F) for no longer than 3 months. During this 3-month period, CAVERJECT Injection may be moved to and kept in a refrigerator at 2° to 8°C (36° to 46°F) for up to 7 days. **Once refrigerated, it must be used within 7 days or discarded; do not refreeze the ampoule.**
- Once removed from the foil wrapping, use the solution in the ampoule immediately after allowing it to warm to room temperature or discard it.
- After opening the ampoule, CAVERJECT Injection should be used immediately.
- During travel, care should be taken to avoid allowing the medicine to be stored at temperatures above 8°C (46°F). Therefore, do not store in checked luggage during air travel or leave in a closed automobile. Transporting your medicine in a cooler with wet ice is recommended. Brief (2 hours or less) exposure to conditions as warm as 25°C (77°F) will not harm your medicine. However, it should be replaced in the refrigerator or freezer as soon as practical.

ADDITIONAL INFORMATION

There is a technical leaflet discussion of CAVERJECT written for health-care professionals that your pharmacist can let you read.

More information about erectile dysfunction and its treatment is available from the National Institutes of Health (Washington, DC), the American Foundation for Urological Diseases (Baltimore, MD), or the impotence institute of America (Washington, DC).

PREPARING AND INJECTING CAVERJECT

You must be properly instructed and trained in the injection technique by your doctor before using CAVERJECT.

Before using CAVERJECT, talk to your doctor about what to expect when using it, possible side effects, and what to do if side effects occur. Your dose has been selected for your individual needs. Do not change your dose without consulting your doctor. If you are not sure of the volume or dose to be used, talk to your doctor or pharmacist.

Follow these instructions exactly to prepare and inject a sterile dose of CAVERJECT.

Use the needle, syringe and ampoule **only once**, then safely discard the supplies and any unused solution (see the "Disposal of Injection Materials" section of these instructions).

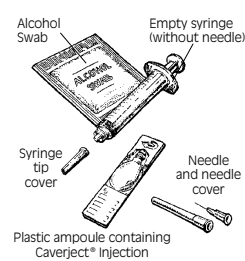
Supplies Needed

Along with an ampoule of CAVERJECT Injection, you will need a needle, a syringe, and an alcohol swab (Figure A). A complete set of these items is available from your doctor or pharmacist, or is supplied in the CAVERJECT Companion Pack.

Two needles of different size are provided in the Companion Pack; a 1/2", 27 gauge needle and a thinner 1/2", 30 gauge needle. Your doctor should advise you on the appropriate needle to use for your injection.

CAVERJECT comes in ampoules containing 10, 20 and 40 micrograms. **MAKE SURE YOU HAVE THE RIGHT STRENGTH AMPOULE OF CAVERJECT.**

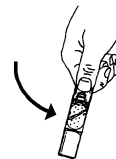
A. Caverject Injection and injection supplies



Prepare the Dose

- Remove an ampoule of CAVERJECT Injection from the foil wrapping. Allow the ampoule contents to warm to room temperature. The ampoule should not be cool to the touch. **Do not immerse in water. Do not microwave.** Once removed from the foil wrapping, use the solution in the ampoule immediately after allowing it to warm to room temperature or discard it.
- Wash your hands thoroughly, and dry them with a clean towel.
- Remove the syringe from its packaging by handling the syringe barrel only. Remove the syringe tip cover, pull the plunger back about half way, and set the syringe aside on a clean surface. Do not touch the tip of the syringe.
- Shake the ampoule vigorously for at least 30 seconds. Next, hold the shorter tab closest to the neck of the ampoule and shake it downward with a quick snap to clear any solution from the neck (Figure B).

B. Shaking fluid from the neck of the ampoule



- Holding the ampoule by the side edges, twist the top of the ampoule and lift upward to remove. Make sure the open ampoule does not touch your hands or any other surface (Figure C).

C. Removing the top of the ampoule



- While continuing to hold the ampoule upright, securely attach to the tip of the syringe, push and twist in a clockwise fashion to assure a snug fit.
- With the ampoule snugly attached, point the syringe upward, push the plunger to expel air in the syringe, and slowly pull back the syringe

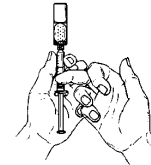
plunger until all of the solution is removed from the ampoule (see Figure D). **DO NOT USE THE SOLUTION IF IT IS CLOUDY, COLORED OR CONTAINS PARTICLES.**

D. Removing fluid from the ampoule



- If there are air bubbles, gently tap the syringe barrel until they float to the top of the solution (see Figure E). Holding the syringe upright, push the syringe plunger until it is slightly below the correct volume mark for the dose prescribed by your doctor. This will expel any air and most of the excess solution back into the ampoule.

E. Tapping the syringe to release air bubbles



- Remove the ampoule from the syringe, place the syringe tip cover on the syringe and set the syringe on a clean surface.
- Two needles of different size are provided in the Companion Pack; a 1/2", 27 gauge needle and a thinner 1/2", 30 gauge needle. Your doctor should advise you on the appropriate needle to use for your injection.
- Remove the selected needle from its package by handling the needle cover only and set on a clean surface.
- Remove the tip from the syringe and attach the needle to the syringe with a twisting movement in a clockwise fashion to assure a tight fit (see Figure F).

F. Attaching needle to syringe



- Grasp the syringe barrel (not the plunger) and carefully remove the needle cover. Do not touch the exposed needle with your hands or any surface.
- Holding the syringe upright, apply extremely gentle upward pressure on the syringe plunger until liquid appears at the tip of the needle. If the syringe plunger is still below the correct volume mark for the dose prescribed by your doctor, any excess solution may be expelled into the open ampoule.
- Place the needle cover over the needle and set the syringe down on a level surface.

Tear along perforated line

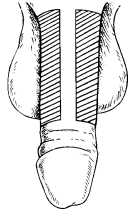
Tear along perforated line

Select Injection Site

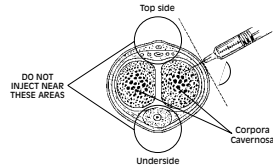
1. CAVERJECT will be injected into a corpus cavernosum (spongy tissue) of the penis. One corpus cavernosum runs the length of the right side of the penis. Another corpus cavernosum runs the length of the left side of the penis (see Figures G and H).

C. Top view of penis

Injection sites (shaded area)



H. Cross-section of penis



2. Choose an injection site on one side of the shaft of the penis as shown in Figure G. AVOID VISIBLE BLOOD VESSELS.
3. WITH EACH USE OF CAVERJECT, ALTERNATE THE SIDE OF THE PENIS AND VARY THE SITE OF THE INJECTION.

Inject Your Dose of CAVERJECT

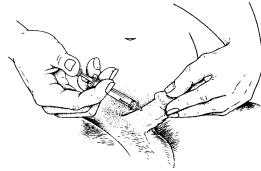
1. You should be sitting upright or slightly reclined when injecting CAVERJECT.
2. If your penis is not circumcised, pull the foreskin back. Holding the head of your penis with your thumb and forefinger, stretch it lengthwise along your thigh so that you can clearly see the selected injection site.
3. Clean the injection site with a new alcohol swab. Do not discard this swab, you will need to use it again (see step 7).
4. Remove the cover from the needle. Reposition the penis firmly against your thigh as in step 2 to keep it from moving during the injection.
5. Hold the syringe between your thumb and index finger (Figure I). Using a steady motion, push the needle straight into the selected site until the metal part of the needle is almost entirely in the penis.

I. Inserting the needle into the injection site



6. Holding the syringe barrel between two fingers, move your thumb or finger to the top of the plunger and, with a steady motion, push down on the plunger so that the entire volume of CAVERJECT is slowly injected (Figure J).

J. Inserting the contents of the syringe



7. Grasp the syringe barrel and pull the needle out of your penis. **APPLY PRESSURE TO THE INJECTION SITE WITH THE ALCOHOL SWAB FOR ABOUT 5 MINUTES OR UNTIL ANY BLEEDING STOPS.**

Disposal of Injection Materials

After use, dispose of all injection materials safely. Your pharmacist may be able to supply a disposal box especially for syringes and needles. **Do not re-use or share needles or syringes. As with all prescription medicines, do not allow anyone else to use your medicine.**

Rx only

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Caverject[®]
(alprostadil injection)
aqueous

**Product
Information**

**Patient
Instructions**