CAVERJECT® **
alprostadil for injection

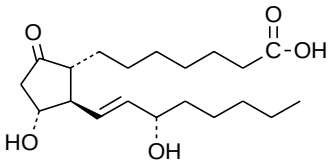
For Intracavernosal Use

DESCRIPTION

CAVERJECT contains alprostadil as the naturally occurring form of prostaglandin E_1 (PGE_1) and is designated chemically as (11α,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid. The molecular weight is 354.49.

Alprostadil is a white to off-white crystalline powder with a melting point between 115º and 116ºC. Its solubility at 35ºC is 8000 micrograms (mcg) per 100 milliliter double distilled water.

The structural formula of alprostadil is represented below:



CAVERJECT ** is available as a disposable, single-dose, dual chamber syringe system. The system includes a glass cartridge which contains sterile, freeze-dried alprostadil in the front chamber and sterile bacteriostatic water for injection in the rear chamber. The alprostadil is reconstituted with the sterile bacteriostatic water just before injection. CAVERJECT ** is available in two strengths for intracavernosal administration:

10 microgram – The reconstituted solution has a volume of 0.64 mL. The delivered volume, 0.5 mL, contains 10 micrograms (mcg) of alprostadil, 324.7 mcg of alpha cyclodextrin, 45.4 mg of lactose, 23.5 mcg of sodium citrate, and 4.45 mg of benzyl alcohol.

20 microgram – The reconstituted solution has a volume of 0.64 mL. The delivered volume, 0.5 mL, contains 20 micrograms (mcg) of alprostadil, 649.3 mcg of alpha cyclodextrin, 45.4 mg of lactose, 23.5 mcg of sodium citrate, and 4.45 mg of benzyl alcohol.

When necessary, the pH of the alprostadil for injection was adjusted with hydrochloric acid and/or sodium hydroxide before lyophilization.

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 $PGF_{2\alpha}$ *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 I-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 alprostadil, peripheral levels of the major circulating metabolite, 13,14-dihydro-15-oxo-PGE_1, 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 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.

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 (± SD) pulmonary extraction of alprostadil was 72% ± 15% in 11 elderly patients aged 65 years or older (mean, 71 ± 6 years) and 65% ± 20% in 6 young patients aged 35 years or younger (mean, 28 ± 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 (± SD) pulmonary extraction was 66% ± 20% in 17 male patients and 69% ± 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: 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 ± 3.2% vs 78 ± 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.

CLINICAL STUDIES

The safety and efficacy of CAVERJECT Sterile Powder was investigated in men with a diagnosis of erectile dysfunction due to psychogenic, vasculogenic, neurogenic, and/or mixed etiology in two well-controlled studies (Study 1 and Study 2) and in one 6-month open-label study (Study 3).

Study 1: One hundred fifty-three men with a mean age of 53 years (range 23-69 years) were enrolled. The study had three phases: a 2.5 week double-blind, in-office randomized crossover phase in which each man received placebo or 2.5 mcg, 5 mcg, 7.5 mcg, or 10 mcg of CAVERJECT Sterile Powder; a 2 week open-label, in-office dose-titration phase to identify the optimum home-use dose (the latter dose was defined as a dose inducing an erection sufficient for penetration and lasting ≤ 60 minutes); and a 4-week open-label, self-injection phase. In the double-blind phase, each dose of CAVERJECT was significantly more effective than placebo by clinical evaluation ("full penile rigidity") and by RigiScan criteria (≥ 70% rigidity for at least 10 minutes); there was no response to placebo. The percentage of responders increased with increasing doses of CAVERJECT. The overall response in the dose-ranging phases was 76% (117/153) by clinical evaluation and 51% (78/152) by RigiScan criteria. The optimum dose for self-injection ranged from 1.25 to 65 mcg (median 20 mcg). Seventy-three percent of the injections in 102 men who self-injected CAVERJECT resulted in satisfactory intercourse. Seventy-five percent of the patients remained on the dose identified during the dose-ranging phase; 17% and 8% of the patients slightly decreased or increased the dose, respectively. The mean duration of erection per injection was 70.8 minutes.

Study 2: Two hundred ninety-six men with a mean age of 53.8 years (range 21-74 years) were enrolled in this parallel-design, double-blind study. The men were randomly assigned to one of five groups and received either a single dose of placebo, 2.5 mcg, 5 mcg, 10 mcg, or 20 mcg of CAVERJECT Sterile Powder. No patient responded to placebo. The differences in the response rates in both the clinical and the RigiScan evaluations between each of the doses of CAVERJECT and placebo were statistically significant. There was also a statistically significant dose-response relationship with higher clinical response rates and higher RigiScan response rates with increasing doses of CAVERJECT (with exception of the 10-mcg dose). The mean duration of erection after injection ranged from 12 minutes after the 2.5-mcg dose to 44 minutes after the 20-mcg dose and the relationship was linear ($p = .025$, linear regression analysis).

Study 3: The safety and efficacy of CAVERJECT Sterile Powder was evaluated in a 6-month, open-label study in 683 men with a mean age of 58 years (range 20-79 years). The optimum dose of CAVERJECT was established by titration in 89% of men (606/683). Four hundred seventy-one men (69%) completed the 6-month study. At the start of the study, the mean dose was 17.7 mcg of CAVERJECT and at the end of the study it was 20.7 mg. Eighty-seven percent of the 13,762

injections of CAVERJECT, administered by self-injection by the men in the study, resulted in satisfactory sexual activity. The mean duration of erection was 67.5 minutes.

The formulation of alprostadil contained in CAVERJECT ** includes the inactive excipient alpha cyclodextrin. This formulation was compared with CAVERJECT Sterile Powder in 87 men in a single-blind, crossover study designed to evaluate efficacy and safety. The doses used by the patients in the study ranged from 2.5 mcg to 20 mcg and were the same for both formulations. The efficacy of the two formulations was shown to be comparable, as assessed by the 30-point erectile function (EF) domain score from the International Index of Erectile Function (IIEF) and by a physician-assessment score for erectile response. The mean EF domain scores for CAVERJECT Sterile Powder and the formulation contained in CAVERJECT ** were 26.6 (SD=5.3) and 27.6 (SD=3.8), respectively. The mean physician's assessment scores for CAVERJECT Sterile Powder and the formulation contained in CAVERJECT ** were 2.6 (SD=0.6) and 2.7 (SD=0.5), respectively, based on a scale of 0 (no tumescence) to 3 (full rigidity).

INDICATION AND USAGE

CAVERJECT (CAVERJECT **, CAVERJECT Sterile Powder, and 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 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.

WARNINGS

Prolonged erection defined as erection lasting > 4 to ≤ 6 hours in duration occurred in 4% of 1,861 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 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

1. CAVERJECT ** is designed for one use only. Following a single use, the injection device and any remaining solution should be properly discarded.

2. 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.

3. Intracavernous injections of CAVERJECT can lead to increased peripheral blood levels of PGE_1 and its metabolites, especially in those patients with significant corpora cavernosa venous leakage. Increased peripheral blood levels of PGE_1 and its metabolites may lead to hypotension and/or dizziness.

4. Patients on anticoagulants, such as warfarin or heparin, may have increased propensity for bleeding after intracavernosal injection.

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

6. 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.

7. CAVERJECT ** uses a superfine (29 gauge) needle. As with all superfine needles, the possibility of needle breakage exists. Careful instruction in proper patient handling and injection techniques may minimize the potential for needle breakage.

8. 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:

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 reconstituted solution with precipitates or discoloration should be discarded. The CAVERJECT ** syringe system is designed for one use only and should be discarded after use. The device and the needle must be properly discarded after use. Needles 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 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 irritancy 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 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.

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 ≥ 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.

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 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.

The safety of CAVERJECT ** was evaluated in a study that compared the formulation of alprostadil for injection contained in CAVERJECT ** with the formulation contained in CAVERJECT Sterile Powder. The doses used by the 87 patients in this crossover study were the same for both formulations. The number and type of events reported for CAVERJECT ** were consistent between formulations in this study and in other controlled and uncontrolled studies with CAVERJECT Sterile Powder.

OVERDOSAGE

Overdosage was not observed in clinical trials with CAVERJECT. If intracavernous 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.

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. The 10 mcg strength of CAVERJECT ** is designed to allow delivery of a 2.5 mcg dose of alprostadil (see General Procedure for Solution Preparation). If there is a partial response at 2.5 mcg, the dose may be increased by 2.5 mcg to a dose of 5 mcg within 1 hour. No more than 2 doses during initial titration should be given within a 24-hour period. If additional titration is required, doses in increments of 5 to 10 mcg may be given at least 24 hours apart 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 within 1 hour. No more than 2 doses during initial titration should be given within a 24-hour period. If additional titration is required, doses in increments of 5 to 10 mcg may be given at least 24 hours apart. The patient must stay in the physician's office until complete detumescence occurs.
Erectile Dysfunction of Pure Neurogenic Etiology (Spinal Cord Injury). Dosage titration should be initiated at 1.25 mcg of alprostadil. Because CAVERJECT ** is designed to deliver doses of 2.5 mcg or greater (see General Procedure for Solution Preparation), CAVERJECT Sterile Powder or CAVERJECT Injection may be used for an initial dose of 1.25 mcg. The initial dose may be increased by 1.25 mcg to a dose of 2.5 mcg within 1 hour. No more than 2 doses during initial titration should be given within a 24-hour period. If additional titration is required, a dose of 5 mcg may be given during the next 24 hours. Thereafter, doses in increments of 5 mcg may be given at least 24 hours apart 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.

The majority of patients (56%) in one clinical study involving 579 patients with erectile dysfunction of various etiologies 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 should 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 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 the physician's office; however, dose adjustment, if required (up to 57% of patients in one clinical study), should 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. CAVERJECT ** in the 10 mcg strength is designed to deliver a minimum dose of 2.5 mcg and a maximum dose of 10 mcg. CAVERJECT ** in the 20 mcg strength is designed to deliver a minimum dose of 5 mcg and a maximum dose of 20 mcg. The physician should determine the most suitable formulation of CAVERJECT for the individual patient (CAVERJECT **, CAVERJECT Sterile Powder, or CAVERJECT Injection).

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. All formulations of CAVERJECT are intended for single use only and should be discarded after use. The user should be instructed in the proper disposal of the injection materials (eg, device, needles).

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, ^{133}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.

General Procedure for Solution Preparation:

CAVERJECT ** consists of a disposable, single-dose, dual-chamber syringe system. The system includes a glass cartridge which contains sterile, freeze-dried alprostadil in the front chamber and sterile bacteriostatic water for injection in the rear chamber. Following proper reconstitution instructions, the 10 mcg strength syringe can deliver up to 0.5 mL of solution. Each 0.5 mL of solution contains 10 mcg of alprostadil, 324.7 mcg of alpha cyclodextrin, 45.4 mg of lactose, 23.5 mcg of sodium citrate, and 4.45 mg of benzyl alcohol. The delivery device can be set to deliver a solution volume of 0.125, 0.25, 0.375, or 0.50 mL to enable administration of 2.5, 5, 7.5, or 10 mcg of alprostadil. Following proper reconstitution instructions, the 20 mcg strength syringe can deliver up to 0.5 mL of solution. Each 0.5 mL of solution contains 20 mcg of alprostadil, 649.3 mcg of alpha cyclodextrin, 45.4 mg of lactose, 23.5 mcg of sodium citrate, and 4.45 mg of benzyl alcohol. The delivery device can be set to deliver a solution volume of 0.125, 0.25, 0.375, or 0.50 mL to enable administration of 5, 10, 15, or 20 mcg of alprostadil. After reconstitution, the solution of CAVERJECT should be used within 24 hours when stored at or below 25^{o}C (77^{o}F). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. The product should not be used if particulate matter or discoloration are present. Following a single use, the injection device and any remaining solution should be properly discarded.

Caution: CAVERJECT ** is for single use only. Do not use any remaining CAVERJECT solution.

HOW SUPPLIED

CAVERJECT ** is supplied as a disposable, single-dose, dual chamber syringe system. The system includes a glass cartridge which contains sterile, freeze dried alprostadil in the front chamber and sterile bacteriostatic water for reconstitution in the rear chamber. The syringes contain either 12.8 or 25.6 mcg of alprostadil to allow delivery of a maximum of 10 or 20 mcg/0.5mL. Store the unreconstituted product at 25°C (77°F); excursions permitted to 15° to 30°C (59 ° to 86°F) [see USP Controlled Room Temperature].

When reconstituted and used as directed, the deliverable amount for the 10 mcg strength is 10 mcg/0.5 mL or an increment of 10 mcg/0.5 mL, 2.5 mcg/0.125 mL, 5.0 mcg/0.25 mL, or 7.5 mcg/0.375 mL of alprostadil and the deliverable amount for the 20 microgram strength is 20 mcg/0.5 mL or an increment of 20 mcg/0.5 mL, 5 mcg/0.125 mL, 10 mcg/0.250 mL, or 15 mcg/0.375 mL of alprostadil. The reconstituted solution should be used within 24 hours when stored at or below 25°C (77°F).

CAVERJECT ** is supplied in a carton containing 2 blister trays. Each blister tray contains one dual chamber syringe system, one needle and 2 alcohol swabs. It is available in the following strengths:

10 mcg	NDC 0009-5181-01
20 mcg	NDC 0009-5182-01

CAVERJECT is also available as follows:

CAVERJECT Sterile Powder (alprostadil for injection) packaged in vials, 6 vials per carton

- 10 mcg NDC 0009-3778-05
- 20 mcg NDC 0009-3701-05
- 40 mcg NDC 0009-7686-04

CAVERJECT Sterile Powder (alprostadil for injection) vials with diluent syringe, 6 syringe systems per carton

- 5 mcg NDC 0009-7212-03
- 10 mcg NDC 0009-3778-08
- 20 mcg NDC 0009-3701-01

CAVERJECT Injection ([alprostadil injection] aqueous), 5 ampoules per carton

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

Rx only

Manufactured for:
Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

By:
Pharmacia AB
Stockholm, Sweden

Date (to be added)
Copy code (to be added)

[NOTE: the insert will contain a perforation to allow the Patient Instructions to be torn-off]

Patient Instructions For:

CAVERJECT® **
alprostadil for injection

Read this information carefully before using CAVERJECT [KAV-er-jeckt]. Read the information you get each time you renew your prescription, in case anything has changed. This is a summary and does not replace talking with your doctor when you start this medication and at check-ups. If you have any questions or concerns, talk to your doctor about them.

What is CAVERJECT?

CAVERJECT is a medicine to treat male impotence (erectile dysfunction). 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 no longer than 1 hour.

CAVERJECT ** is for one use only and should be thrown away properly after a single use.

CAVERJECT does not protect you from sexually transmitted diseases (STDs), such as HIV (the virus that causes AIDS). In addition, small amounts of bleeding at the injection site can increase the risk of passing diseases carried by the blood, such as HIV.

What are the causes of and treatments for impotence?

There are several causes of impotence. These include medications that you may be taking for other conditions, poor blood circulation in the penis, nerve damage, emotional problems, too much smoking or alcohol use, use of street drugs, and hormonal problems. Often, impotence is due to more than one cause.

Treatments for impotence include switching medications if you are taking a medication that causes impotence, prescription medications, medical devices that produce an erection, surgical procedures to correct blood flow in the penis, penile implants, and psychological counseling.

You should not stop taking any prescription medications, unless told to do so by your doctor.

The use of other medical treatments for impotence in combination with CAVERJECT is not recommended. Discuss any concerns you may have about combination treatment with your doctor.

Who should not use CAVERJECT?

Do not use CAVERJECT if you have certain conditions that might cause long-lasting erections (lasting more than 4 hours). Long-lasting erections may cause penis damage. These conditions include:

- sickle cell anemia or trait
- leukemia
- tumor of the bone marrow (multiple myeloma)

Do not use CAVERJECT if you
- have a penile implant
- have an abnormally formed penis
- have other penis problems
- were told by your doctor not to have sex

Women and children should not use CAVERJECT.

How should I use CAVERJECT?

You will be treated with CAVERJECT in your doctor's office to find out what dose is best for you. After that, you can inject it yourself at home. Do not use it more than 3 times a week. There should be at least 24 hours between doses. See your doctor for regular check-ups to be sure CAVERJECT is not causing damage and that it is working as well as possible.

See the section "Instructions for Use" at the end of this leaflet for details about how to use CAVERJECT.

What are the possible side effects of CAVERJECT?

About 4 in 100 men who use CAVERJECT may get erections that last more than 4 hours. These 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.

You may get a small amount of bleeding at the injection site. This is more likely if you have a medical condition or are taking a medicine that interferes with blood clotting.

Call your doctor if you notice any redness, lumps, swelling, tenderness, or curving of the erect penis. Also, tell your doctor about any penis pain you did not have before or other penis problems you have.

There is a possibility of needle breakage with use of CAVERJECT **. To best avoid breaking the needle, you should pay careful attention to your doctor's instructions and try to handle the device properly. If the needle breaks during injection and you are able to see and grasp the broken end, you should remove it and contact your doctor. If you cannot see or cannot grasp the broken end, you should promptly contact your doctor.

How should I store CAVERJECT **?

1. Unmixed packages of CAVERJECT **, should be stored at room temperature. Temperatures between 59° to 86°F (15° to 30°C) are allowed. Avoid storing CAVERJECT ** at very high and very low temperatures.

2. During travel, do not let the medicine freeze or be stored at a temperature above 77°F (25°C). For example, do not store it in checked luggage during air travel or leave it in a closed automobile.

3. After mixing, CAVERJECT ** should be used within 24 hours. It should be kept at a temperature of 77°F or below during this storage time.

General advice about prescription medicines

Medicines are sometimes prescribed or purposes other than those listed in a Patient Information Leaflet. If you have any concerns about CAVERJECT, ask your doctor. Your doctor or pharmacist can give you information about CAVERJECT that was written for health care professionals. Do not use CAVERJECT for a condition for which it was not prescribed. Do not share CAVERJECT with other people.

You can get more information about impotence (erectile dysfunction) and its treatment from the National Institutes of Health (Washington, DC), the American Foundation for Urological Diseases (Baltimore, MD), or the Impotence Institute of America (Washington, DC).

. . . .

INSTRUCTIONS FOR USE

Before you use CAVERJECT, your doctor must train you in how to prepare and give the injection properly.

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 (germ-free) dose of CAVERJECT.

Supplies Needed

CAVERJECT ** is packaged with a needle for injection (Figure A) and alcohol swab.

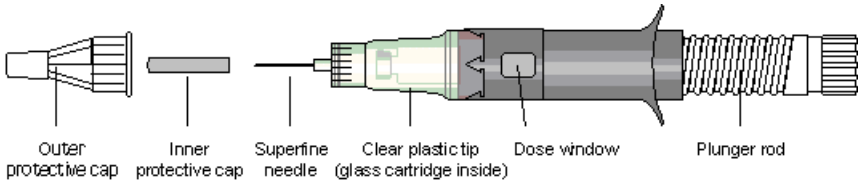


Figure A

CAVERJECT ** is available in 10 and 20 mcg strengths. **MAKE SURE YOU HAVE THE RIGHT STRENGTH OF CAVERJECT **.**

Prepare the Dose

1. Wash your hands thoroughly and dry them with a clean towel.

2. Remove the device, needle, and alcohol swabs from the blistered tray.

3. Using one of the alcohol swabs, clean the rubber membrane at the tip of the syringe (Figure B).

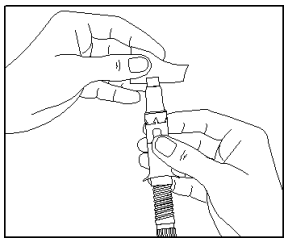


Figure B

4. Peel the paper lid from the needle (Figure C).

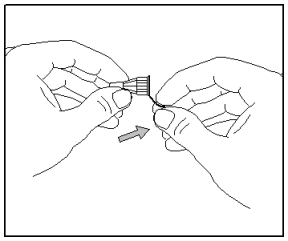
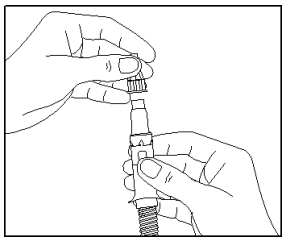


Figure C

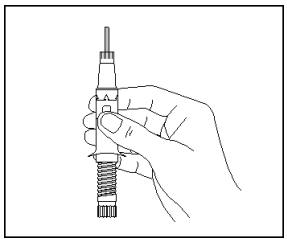
5. Attach the needle to the device by pressing the needle on to the tip of the device and turning clockwise until the needle is firmly in place. Remove the outer protective cap from the needle (Figure D).

Figure D



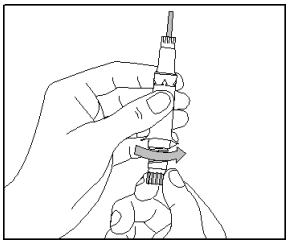
6. Hold the device with the needle pointing upward. The white plunger rod is in the extended position (Figure E).

Figure E



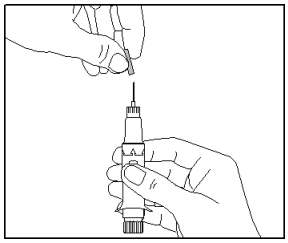
7. Turn the plunger rod slowly clockwise until it stops. This automatically mixes the alprostadil powder and the diluent. Turn the device upside down several times to make sure the solution is evenly mixed. The solution should be clear. Do not use it if it is cloudy or contains particles (Figure F).

Figure F



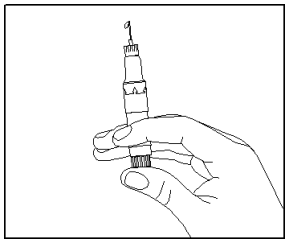
8. Hold the device with the needle upward and carefully remove the inner protective cap from the needle (Figure G).

Figure G



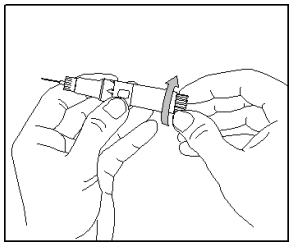
9. Keeping the device upright, press the plunger rod as far as it will go. A few drops will appear at the needle point and the solution will be free of bubbles although typically there may be some very small bubbles at the side of the glass cartridge (Figure H).

Figure H



10. Turn the end of the plunger rod clockwise slowly to choose the dose your physician has determined is appropriate for you. The number that appears in the window shows the dose in micrograms. If the number is higher than your prescribed dose, continue to turn the plunger rod clockwise slowly until you reach the correct dose (Figure I).

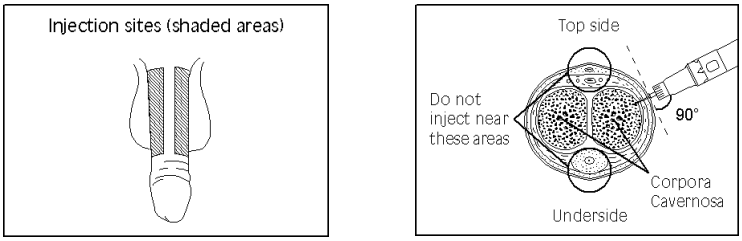
Figure I



11. Set the device down on a level surface making sure the needle is not in contact with the surface.

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 J and K).



Figures J and K

2. Choose an injection site on one side of the shaft of the penis as shown in Figure J. **Avoid visible veins**.

3. **With each use of CAVERJECT, alternate the side of the penis and vary the site of injection.**

Inject Your Dose of CAVERJECT

1. You should be sitting upright or slightly reclined when injecting CAVERJECT.

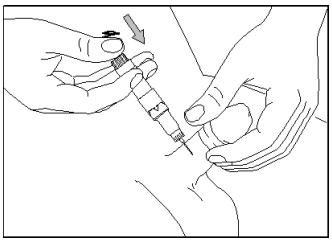
2. Holding the head of your penis with your thumb and forefinger, stretch your penis lengthwise along your thigh so that the skin is tight and you can clearly see the selected injection site.

3. Clean the injection site with a new alcohol swab. Do not discard this swab, you will need to use it again (see step 6).

4. Reposition the penis firmly against your thigh as in step 2 to keep it from moving during the injection.

5. Holding the device between your thumb and index finger, push the needle into the selected site through the skin and into the tissue as far as it will go. Push the plunger rod as far as it will go so the entire dose is injected (Figure L). If the injection solution does not flow easily, move the needle slightly and push as before. When using a dose less than the full capacity, a small amount of liquid will remain in the device.

Figure L



6. Grasp the device and pull the needle out of your penis. **Push on the injection site with the alcohol swab for about 5 minutes or until any bleeding stops.**

7. Carefully replace the outer protective cap on the needle.

Disposal of Injection Materials

After use, dispose of all injection materials safely. Your pharmacist may be able to supply a disposal box especially for disposable injection devices. **As with all prescription medicines, do not allow anyone else to use your medicine.**

Rx only

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A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

By:
Pharmacia AB
Stockholm, Sweden

Date (to be added)
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/s/

Daniel A. Shames

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