

## **PRODUCT MONOGRAPH**

### **PrCAVERJECT® STERILE POWDER**

(Alprostadil for Injection)

20 mcg Vials

#### **Prostaglandin**

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## PRODUCT MONOGRAPH

### <sup>Pr</sup>CAVERJECT STERILE POWDER (Alprostadil for Injection)

#### Prostaglandin

### ACTION AND CLINICAL PHARMACOLOGY

Alprostadil is a prostaglandin with various pharmacological actions that include vasodilation and inhibition of platelet aggregation, inhibition of gastric secretion, stimulation of intestinal smooth muscle and stimulation of uterine smooth muscle.

Alprostadil, when given to impotent men by intracavernous injection, induces erections within 5 to 20 minutes after administration. The duration of erection is dose-dependent. The mechanism of penile erection involves a complex series of neurovascular events. Alprostadil injected intracavernosally causes tumescence by increasing cavernous blood flow through relaxation of trabecular smooth muscle and dilation of cavernosal arteries.

With regards to the action of alprostadil on penile structures, in most animal species tested, alprostadil had relaxant effects on 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 previously contracted by either noradrenaline or PGF<sub>2α</sub>.

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.

Other actions of PGE<sub>1</sub> involve the cardiovascular system, central nervous system (CNS), autonomic nervous system, respiratory system, gastrointestinal system and hematopoietic system.

#### Pharmacokinetics

##### Absorption

The absolute bioavailability of alprostadil following intracavernosal injection has not been determined.

##### Distribution

Following a 20 mcg intracavernosal injection of alprostadil, mean peripheral plasma concentrations of alprostadil were 89 pg/mL and 102 pg/mL at 30 and 60 minutes post injection respectively, which were not significantly greater than baseline levels of endogenous alprostadil at 96 pg/mL. Alprostadil is bound primarily to plasma albumin (81%) and to a lesser degree to α-globulin IV-4 fraction (55%). No significant binding could be demonstrated with erythrocytes or white cells.

##### Metabolism

Alprostadil is rapidly converted to compounds which are further metabolized prior to excretion. In man, a single pass through the lung effectively metabolizes approximately 80% of the available PGE<sub>1</sub> primarily by *beta*- and *omega*-oxidation. Therefore, any alprostadil which may enter the systemic circulation following

intracavernosal injection is rapidly metabolized. However, pulmonary clearance of PGE<sub>1</sub> can be affected by disease states such as acute respiratory distress syndrome (ARDS), with a resultant reduction in the pulmonary extraction ratio.

After intracavernosal administration of 20 mcg of alprostadil, peripheral levels of the primary metabolite 15-oxo-13,14-dihydro-PGE<sub>1</sub> increased, reaching a peak at 30 minutes and falling to pre-dose levels by 60 minutes post injection.

#### Excretion

The major route of elimination of the metabolites of alprostadil is through the kidney. Urinary excretion of an intravenous dose is essentially complete (90%) within 24 hours of administration. The remainder of the dose is excreted in the feces. There is no evidence to suggest any tissue retention of PGE<sub>1</sub> or its metabolites after an 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 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

Caverject contains the diluent benzyl alcohol and is contraindicated in children and newborns (see the Contraindications and Warnings sections).

Plasma alprostadil concentrations were evaluated in 10 neonates (gestational age 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. Alprostadil infusion rates ranged from 5 to 50 ng/kg/min (median 45 ng/kg/min), with resultant plasma concentrations in the range of 22 to 530 pg/mL (median 56 pg/mL). The individual clearance of alprostadil in neonates is highly variable as reflected by the wide range of plasma concentrations observed.

#### Gender

The influence of gender on the pharmacokinetics of alprostadil has not been formally studied. Two studies evaluated pulmonary extraction in 23 patients with ARDS following intravenous administration of alprostadil. The 17 males had a pulmonary extraction of 66% compared to 69% in the 6 female patients, suggesting no gender influence.

#### Race

The influence of race on the pharmacokinetics of alprostadil has not been formally studied.

#### Renal and Hepatic Insufficiency

The effects of renal and hepatic insufficiency on the pharmacokinetics of alprostadil have not been formally studied. Since systemic clearance of alprostadil is primarily by first-pass metabolism through the lungs, it is not expected that altered renal or hepatic function will have a major influence on the pharmacokinetics of alprostadil.

### Pulmonary Disease

In one study, pulmonary extraction of alprostadil given intravenously was found to be reduced by 15% in patients with ARDS (66%) compared to patients with normal respiratory function (78%). In a second study of 14 patients with ARDS or at risk of developing ARDS, the mean extraction efficiency of alprostadil was 67% ranging from subnormal (11%) to normal (90%).

## INDICATIONS AND CLINICAL USE

CAVERJECT (alprostadil) is indicated for the intracavernosal treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology. Intracavernosal CAVERJECT may also be useful as an adjunct to diagnostic tests in the diagnosis of erectile dysfunction.

CAVERJECT is not indicated for pediatric use (*See Contraindications*).

## CONTRAINDICATIONS

CAVERJECT (alprostadil) is contraindicated in the following individuals:

1. Patients with a known hypersensitivity to the drug.
2. Patients who have any condition that may predispose them to priapism such as sickle cell anemia or trait, multiple myeloma or leukemia.
3. Patients with anatomical deformations of the penis, such as angulation, cavernosal fibrosis, Peyronie's disease.
4. Patients with penile implants.

CAVERJECT should not be used in women or children and is **not for use in newborns**.

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

## WARNINGS

Prolonged erection (4 to 6 hours) and/or priapism (>6 hours) are known to occur following intracavernosal administration of vasoactive substances, including CAVERJECT (alprostadil). In clinical studies, prolonged erection occurred in 4% of patients and 0.4% experienced priapism.

The patient should be instructed to immediately report to his physician, or if unavailable, to seek immediate medical assistance for an erection persisting more than 3 hours. Treatment of prolonged erection/priapism should be according to established medical practice (*see Symptoms and Treatment of Overdosage*). If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

In the majority of cases, spontaneous detumescence occurred. To minimize the chances of prolonged erection or priapism, CAVERJECT should be titrated slowly to the lowest effective dose (*see Dosage and Administration*).

The diluent that is used to reconstitute CAVERJECT contains benzyl alcohol, a preservative that has been associated with serious adverse events, including the “gasping syndrome”, and death in pediatric patients. The minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys’ capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

Benzyl alcohol can cross the placenta.

## PRECAUTIONS

### General

- a) Underlying treatable medical causes of erectile dysfunction must be diagnosed and treated prior to initiating therapy with CAVERJECT (alprostadil).
- b) The results of clinical studies with CAVERJECT indicate an overall incidence of penile fibrosis, including Peyronie's disease, of 3% (55/1861). In one long-term (up to 18 months duration) self-injection study, the incidence of fibrosis reported was 7.8% (53/683). 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.
- c) Patients on anticoagulants such as warfarin or heparin may have an increased propensity for bleeding after intracavernosal injection.
- d) An injection of CAVERJECT can induce a small amount of bleeding at the injection site (*see Adverse Reactions- hematoma, ecchymosis, hemorrhage*). In patients infected with blood-borne diseases, this may increase the transmission of blood-borne diseases between partners.
- e) 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.

### Drug Interactions

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

### Information to be Provided to Patient

- a) Patients using a self-injection program of therapy should receive proper instruction in both intracavernosal injection and aseptic technique (*see Information for the Consumer*). Physicians should ensure that patients are able to demonstrate competence and skill with the injection procedure prior to initiating self-injection.
- b) CAVERJECT uses a superfine needle for administration. As with all superfine needles, the possibility of needle breakage exists.

Needle breakage, with a portion of the needle remaining in the penis, has been reported and, in some cases, required hospitalization and surgical removal.

Careful patient instruction in proper handling and injection techniques may minimize the potential for needle breakage.

The patient should be instructed that, if the needle is bent, it must not be used; they should also not attempt to straighten a bent needle. They should remove the needle from the syringe, discard it, and attach a new, unused sterile needle to the syringe.

- c) The initial treatment dose is established in the physician's office. The lowest effective dose sufficient to induce an erection lasting up to 1 hour should be used. The patient may expect an erection to occur within 5 to 20 minutes. Patients who require dosage adjustments and are self-injecting CAVERJECT, should not increase or decrease their dose without the advice of their physician. Generally, patients should not use CAVERJECT more than once a day and not more than 3 times a week, with at least 24 hours between each use.
- d) CAVERJECT is labelled for "single use only", patients should discard any unused solution after withdrawing the proper volume for their dose. The vial should not be shaken once reconstituted.
- e) Reconstituted vials of CAVERJECT which on visual inspection appear cloudy, coloured or contain particulate matter, should be discarded.
- f) Patients who experience an erection lasting longer than 2 hours should attempt to detumescence using methods prescribed by their physician.
- g) Patients should be advised on the possible adverse effects associated with the use of CAVERJECT; the most frequent being mild to moderate penile pain after injection. A patient should report to his physician if he complains of: any penile pain not previously present, an increased intensity of pain, nodules or hard tissue appearing in the penis, or curvature of the erect penis. There is the potential for infection with any type of injection, therefore patients should also report any occurrences of penile redness, swelling, or tenderness. The importance of regular physician visits to assess the continued safety and efficacy of CAVERJECT treatment should be stressed to the patient.

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 3 hours.

- h) In clinical trials, the use of concomitant medicines such as antihypertensives, diuretics, antidiabetic agents (including insulin) or non-steroidal anti-inflammatory drugs, did not affect the safety or efficacy of CAVERJECT.
- i) The use of CAVERJECT intracavernosally does not offer any protection from the spread of sexually transmitted diseases. Individuals using CAVERJECT should be properly counselled with regards to protective measures to safeguard against the spread of sexually transmitted diseases, including human immunodeficiency virus (HIV) infection.
- j) Patients should be instructed not to reuse or share needles or syringes. The patient should not allow anyone else to use this medicine. Patients should dispose of used needles, syringes, and vials, safely and properly. (*see Information for the Consumer*)

- k) A patient administration guide, found in every package of CAVERJECT, provides a step-by-step method for the proper preparation and administration of CAVERJECT. Patients should be instructed to carefully follow this guide for self-injection.

#### **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

Long-term carcinogenicity studies have not been conducted. Reproductive studies in the rat with alprostadil at doses of up to 0.2 mg/kg/day did not adversely affect or alter spermatogenesis, conferring a 200-fold margin of safety at usual human doses. A battery of mutagenicity assays including, bacterial mutation (Ames), alkaline elution, rat micronucleus, sister chromatid exchange, CHO/HGPRT mammalian cell forward gene mutation and unscheduled DNA synthesis (UDS), revealed no potential for mutagenesis. (*see Toxicology*).

A 1 year irritancy study was conducted in male Cynomolgus monkeys. Three groups of 5 animals received twice weekly intracavernosal injections of either 3 or 8.25 mcg alprostadil or vehicle. A further 2 groups of 6 animals were given 8.25 mcg alprostadil or vehicle twice weekly, as above, and in addition, multiple doses during weeks 44, 48 and 52. Three monkeys receiving vehicle and 3 monkeys receiving 8.25 mcg alprostadil were held for evaluation following a 4 week recovery period. No evidence of alprostadil-related penile or systemic tissue lesions was found. Local irritation noted in control and treated monkeys was considered to be related to the injection procedure itself and any penile lesions found were reversible. After the 4 week recovery period, a regression in histological changes in the penis was observed. (*see Local Tolerance*)

## ADVERSE REACTIONS

### Local Adverse Events

The following local adverse events were reported from controlled and uncontrolled clinical trials, including an uncontrolled 18 month safety study.

Local Event (reported in ≥1% of patients)	No. (%) of Pts (N=1861)	
Penile Pain	696	(37)
Pain after injection	580	(31)
Pain at the injection site	370	(20)
Prolonged erection (4-6 hr)	82	(4)
Penile fibrosis <sup>a</sup>	55	(3)
Injection site hematoma	63	(3)
Penis disorder <sup>b</sup>	46	(3)
Injection site ecchymosis	32	(2)
Penile rash	21	(1)
Penile edema	18	(1)

<sup>a</sup> Includes generalized or deep fibrosis, penile curvature/deviation, and Peyronie's disease.

<sup>b</sup> Includes numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, erythema, venous leak, penile skin tear, strange feeling in penis, burning sensation in penis and itch at tip of penis.

#### Penile Pain

Penile pain after intracavernosal administration of CAVERJECT (alprostadil) was reported at least once by 37% of patients in clinical studies of up to 18 months in duration. The intensity of pain was rated mild or moderate in the majority of cases. 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 (*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*).

Local events observed in <1% of the patients include: balanitis, lack of efficacy, injection site hemorrhage, injection site inflammation, injection site itching, injection site reaction, injection site swelling, injection site edema, trauma, urethral bleeding, urethral disorder, penile hematoma, penile warmth, priapism (>6 hr), 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, including an uncontrolled 18 month safety study.

Systemic Event <sup>a</sup> by Body System <sup>b</sup> (reported in ≥1% of patients) <sup>c</sup>	No. (%) of Pts (N=1861)	
BODY AS A WHOLE	245	(13)
Upper respiratory infection	76	(4)
Flu syndrome	42	(2)
Headache	37	(2)
Trauma <sup>d</sup>	33	(2)
Localized pain <sup>e</sup>	32	(2)
Back pain	22	(1)
Localized abdominal pain	10	(<1)
RESPIRATORY	123	(7)
Sinusitis	43	(2)
Nasal congestion	25	(1)
Cough	21	(1)
Bronchitis	18	(1)
Pharyngitis	16	(<1)
UROGENITAL	121	(7)
Prostatic disorder <sup>f</sup>	28	(2)
Urinary tract infection	16	(<1)
Testicular pain	16	(<1)
Hematuria	10	(<1)
CARDIOVASCULAR	80	(4)
Hypertension	39	(2)
CENTRAL NERVOUS	66	(4)
Dizziness	22	(1)
DIGESTIVE	86	(5)
Nausea	14	(<1)
Tooth abscess	12	(<1)
Diarrhea	11	(<1)
Dyspepsia	11	(<1)
SKIN AND APPENDAGES	49	(3)
Rash	11	(<1)

<sup>a</sup> number (%) patients reporting the event, with patients reporting the same event more than once counted only once.

<sup>b</sup> number (%) patients reporting a drug-related event within body system, with patients reporting more than one event within the body system counted only once.

<sup>c</sup> no significant adverse events were reported by 294 patients who received 1 to 3 injections of placebo.

<sup>d</sup> includes injuries, fractures, abrasions, lacerations, dislocations.

<sup>e</sup> includes pain in various anatomical structures other than injection site.

<sup>f</sup> includes prostatitis, pain, hypertrophy, enlargement.

Systemic events reported in 1% of patients and judged by investigators to be possibly related to the use of CAVERJECT include: testicular pain, scrotal disorder, scrotal edema, hematuria, testicular disorder, impaired urination, urinary frequency, pelvic pain, hypotension, vasodilation, peripheral vascular disorder, supraventricular extrasystole, vasovagal reactions, hypoesthesia, 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 clinically unimportant; only three patients discontinued the treatment because of symptomatic hypotension.

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

### **Post-Market Adverse Drug Reactions**

The following adverse event was reported during Post-Marketing Surveillance:

- Urogenital: Urinary urgency

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

The pharmacotoxic signs of alprostadil are similar in all animal species and include depression, soft stool or diarrhea and rapid breathing. In mice, the lowest acute LD<sub>50</sub> was 12 mg/kg which is 12,000 times greater than the maximum recommended human dose of 60 mcg.

In man, prolonged erection and/or priapism are known to occur following intracavernosal administration of vasoactive substances.

Given the dose-response relationship of alprostadil with erection duration, the therapeutic dose range should be determined individually for each patient by his physician during the initial office instruction.

Inadvertent or intentional overdosing is the most common cause of prolonged pharmacological erection. In clinical trials with CAVERJECT (alprostadil), overdosage was not observed. 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.

Patients should be instructed to report any erections persisting for more than 3 hours to a physician. The treatment of priapism/prolonged erection should be according to established medical practice. Physicians may refer to two suggested protocols for detumescence presented below.

### Detumescence Protocols

1. Aspirate 40 to 60 mL from either right or left corpora using vacutainer and holder as for drawing blood. Use landmarks as for intracavernosal injection. Patient will often detumescence while aspirating. Apply ice for 20 minutes post aspiration if erection remains.

If 1) unsuccessful then,

2. Have patient in supine position. Dilute 10 mg phenylephrine into 20 mL water for injection (0.05%). With an insulin syringe, inject 0.1 to 0.2 mL (50-100 mcg) into the corpora every 2 to 5 minutes, until detumescence occurs.

The occasional patient may experience very transient bradycardia and hypertension when given phenylephrine injections, therefore monitor patient's blood pressure and pulse every 10 minutes. Patients at risk include those with cardiac arrhythmias and diabetics. Refer to the prescribing information for phenylephrine before use.

DO NOT give to patients on MAO inhibitors. When phenylephrine is used within the first 12 hours of erection, the majority of patients will respond.

3. If the above measures fail to detumescence the patient, a urologist should be consulted as soon as possible, especially if the erection has been present for many hours. If priapism is not treated immediately, penile tissue damage and/or permanent loss of potency may result.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## DOSAGE AND ADMINISTRATION

### Administration

CAVERJECT (alprostadil) is administered by direct intracavernosal injection. A 1/2-inch 27- to 30-gauge needle is generally recommended. CAVERJECT is injected into either of two corpora cavernosum along the dorso-lateral aspects of the proximal third of the penis. Avoid any area where there are visible veins. The injection site should be changed for each injection (i.e. alternate sides of penis). Within either area, the point of injection should also be changed each time and the injection site must be cleansed with an alcohol swab.

The diluent that is used to reconstitute CAVERJECT contains benzyl alcohol (*see Contraindications and Warnings*).

### Therapeutic/Effective Dose

Appropriate initial doses and maintenance doses are recommended based on the etiology of the erectile dysfunction. In all cases, the dose should be titrated on an individual basis by the physician, and the lowest effective dose always employed as the therapeutic dose. An effective dose is defined as one which produces an erection sufficient for intercourse with an erection duration not exceeding 1 hour.

The following guidelines for dose titration are 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 effective dose is reached (*see Therapeutic/Effective Dose*). 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 remain in the physician's office until complete detumescence is achieved. 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 24 hour interval before the next dose is given.

*Erectile Dysfunction of Pure Neurogenic Etiology.* 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 effective dose is reached (*see Therapeutic/Effective Dose*). The patient must remain in the physician's office until complete detumescence is achieved.

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 24 hour interval before the next dose is given.

In one clinical study involving 579 patients, the majority of patients (56%) were titrated to doses of >5 mcg but ≤20 mcg. The mean dose at the end of the titration phase was 17.8 mcg of alprostadil.

#### Maintenance Therapy

The initial injection of CAVERJECT must be delivered by a medically trained health care professional. Before beginning a self-injection program of therapy, the physician must ensure that the patient (or his partner) aptly demonstrates skill and competence with the injection procedure, and uses appropriate sterile technique. A patient package insert is available to patients for referral (*see Information for the Consumer*).

The dose selected for self-injection therapy is established during dose titration in the physician's office. The correct dose is the lowest effective dose. The dose should be reduced if the erection persists for longer than 1 hour; however, the physician should take into consideration the patient's preferences when defining the dose for self-injection. An erection lasting >3 hours is to be treated as a medical emergency. A physician should be consulted for any dose adjustments, if required. The dose should be adjusted in accordance with the titration guidelines described above. Regular follow-up visits, at least every 3 months, are recommended in order to assess the safety and efficacy of the therapy.

#### Maximum Recommended Dose Limits

- Daily dose should not exceed 60 mcg.
- NOT more than once daily and NOT more than 3 times weekly, with at least 24 hours between each dose.
- Do not inject CAVERJECT into an erect penis.

There is no evidence that tolerance to the effects of CAVERJECT develops with continued use. The long-term use of CAVERJECT has been documented for up to 6 months in an uncontrolled self-injection study. The mean dose after 6 months was 20.7 mcg.

A vial of CAVERJECT delivers one dose only. Instructions for proper disposal of the syringe, needle and vial should be followed (*see Information for the Consumer*).

## **Diagnostic Dose**

### Pharmacologic Testing

An initial dose of 2.5 mcg is employed with subsequent upward titration in 2.5 mcg increments. Patients are monitored for the occurrence of an erection following an intracavernosal injection of CAVERJECT.

### Adjunct to Laboratory Investigations

A single dose of CAVERJECT sufficient to induce a rigid erection is used. For use with Doppler imaging/Duplex Ultrasonography, <sup>133</sup>Xenon washout tests, Radionuclide Phallography and Penile Arteriography for the visualization and assessment of the penile vasculature.

## PHARMACEUTICAL INFORMATION

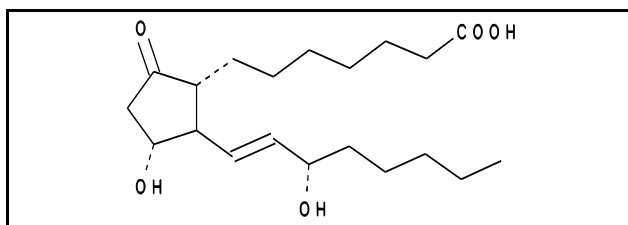
### Drug Substance

Proper Name: alprostadil (INN;USAN;BAN;JAN)

Chemical Name: (11 $\alpha$ , 13E, 15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid.

Empirical Formula: C<sub>20</sub>H<sub>34</sub>O<sub>5</sub>.

Structural Formula:



Molecular Weight: 354.49

Description:

- an odourless, white to off-white crystalline powder.
- melting point of 115E to 116EC.
- acid dissociation constant ( $K_a$ ) is  $1.1 \times 10^{-5}$
- solubility is 80 mcg/mL in water at 35EC.
- pH of 5.15 with 52 mcg/mL alprostadil in deaerated water at 23EC.
- partition coefficient of 0.7 in soyabean oil/water.

### Composition

CAVERJECT STERILE POWDER

STERILE POWDER Ingredients	20 mcg Vial	
	Dry Powder (per vial)	Reconsti- tuted (per mL)
Alprostadil	23.2 mcg	20 mcg
Lactose Monohydrate	193.8 mg	172 mg
Sodium Citrate Dihydrate	53 mcg	47 mcg
10% Hydro- chloric Acid	pH adj.	-
10% Sodium Hydroxide	pH adj.	-

DILUENT Ingredients	Syringe Amount (per mL)	After Vial Reconstitution (per mL)
Benzyl Alcohol	9.45 mg	8.4 mg
Sterile Water for Injection	qs ad	-

### Stability and Storage Recommendations

#### CAVERJECT STERILE POWDER

The unreconstituted lyophilized sterile powder (20 mcg vials) should be stored between 2°C to 30°C.

#### Reconstituted Solutions

CAVERJECT STERILE POWDER (alprostadil for injection) is reconstituted with the addition of 1 mL bacteriostatic water for injection (BWFI). Vial content after reconstitution is approximately 1.13 mL which allows 1.0 mL to be delivered to the patient. An excess of alprostadil is added to compensate for loss due to adsorption to the vial and syringe. The resultant solution contains 20 mcg/mL of alprostadil, 172 mg/mL lactose, 47 mcg/mL sodium citrate, and 8.4 mg/mL benzyl alcohol. Once reconstituted, no additional substances should be injected into the vial.

Once reconstituted, the alprostadil solution must be used immediately. Do not freeze the reconstituted solution. A solution which appears cloudy, coloured or contains particles should be discarded.

#### Parenteral Products (CAVERJECT STERILE POWDER)

Vial Amount	Volume of Diluent Added	Nominal Concentration
23.2 mcg	1 mL BWFI	20 mcg/mL

### AVAILABILITY OF DOSAGE FORMS

CAVERJECT is available in cartons containing 5 cases.

Each case contains: a single dose vial of 20 mcg CAVERJECT sterile powder, 1 mL pre-filled syringe of BWFI diluent, a 27-gauge, 0.5-inch needle, 2 alcohol swabs and Patient Administration Leaflet. These cases are fitted with a lock designed for safe and convenient disposal of the contents after use.

## PHARMACOLOGY

### Pharmacodynamics

The actions of PGE<sub>1</sub> involve the cardiovascular system, central nervous system (CNS), autonomic nervous system, respiratory system, gastrointestinal system and hematopoietic system.

*Cardiovascular.* PGE<sub>1</sub> uniformly lowers the blood pressure of animals when administered intravenously in doses between 1 and 10 mcg/kg. The depressor action is due to a decrease in peripheral resistance. Associated with this are an increased cardiac output and heart rate. The effect of PGE<sub>1</sub> on the cerebral circulation is controversial. Only a low potential exists that intrapenile PGE<sub>1</sub> could induce a cardiovascular change since very limited systemic circulation occurs.

*Central Nervous System.* Prostaglandins are normally present in CNS tissue and exert potent and varied actions. The mechanisms are poorly understood but may be associated with increased cAMP levels. Large doses (7-20 mcg/kg in cats, 25-50 mcg/kg in monkeys) of PGE<sub>1</sub> given by intraventricular injection has sedative effects in animals. The relevance of this pharmacologic activity to peripherally administered PGE<sub>1</sub> is questionable since only minute amounts of PGE<sub>1</sub> are taken up by the nervous tissue. PGE<sub>1</sub> injected into the hypothalamus produces an elevation in body temperature.

*Autonomic Nervous System.* PGE<sub>1</sub> appears to inhibit norepinephrine release from adrenergic nerve endings and inhibits effector responses resulting from adrenergic nerve stimulation.

Cholinergic responses are generally enhanced by PGE<sub>1</sub>, with the exceptions of the heart and gastric mucosa. PGE<sub>1</sub> generally stimulates gastrointestinal smooth muscle and antagonizes sympathomimetic effects on smooth muscle.

*Respiratory System.* PGE<sub>1</sub> inhibits bronchial muscle tone in animals and man when administered by aerosol. Infusion of PGE<sub>1</sub> reduces arterial pulmonary pressure in dogs. The actions of PGE<sub>1</sub> in the respiratory system are brief since the lung is capable of extensive metabolism. In guinea pigs and dogs, a single pass through the lungs removes 90% of PGE<sub>1</sub> from the circulation within minutes.

*Gastrointestinal.* In rats, guinea pigs, cats and dogs, PGE<sub>1</sub> inhibits gastric acid secretion by direct action on the mucosa rather than by effecting mucosal blood flow. In contrast, PGE<sub>1</sub> stimulates intestinal secretion. Intra-arterial infusion of PGE<sub>1</sub> in dogs (0.01-1 mcg/min) and cats (1 mcg/mL) also decreased jejunal motility. Intra-jejunal PGE<sub>1</sub> (0.9 mcg/kg/min) administered to humans had the effect of reversing the net absorption of water and electrolytes. The role of prostaglandins in diarrhea however, is not established. PGE<sub>1</sub> has no effect on salivary secretion in dogs. No consistent effect of PGE<sub>1</sub> on insulin secretion is apparent.

*Hematopoietic.* PGE<sub>1</sub> strongly inhibits ADP-induced platelet aggregation in rat, pig and human plasma. In humans and animals no inhibition is produced at doses of 0.1 and 0.2 mcg/kg/min.

### Pharmacokinetics

PGE<sub>1</sub> is a natural constituent of many mammalian tissues and fluids including the semen of fertile men. The disposition of PGE<sub>1</sub> following intrapenile or intracavernosal injection in laboratory animals has not been studied, however, the disposition has been extensively studied following systemic (intravenous) administration and results of those studies are described briefly.



### Distribution

*Distribution From Plasma.* PGE<sub>1</sub> is rapidly distributed and metabolized throughout the entire body with the exception of the CNS where distribution is limited. Metabolism of PGE<sub>1</sub> in a single pass through the lung is extensive, amounting to approximately 80% in man, 87-95% in dogs, 90% in cats and rabbits, 88% in rats and 73% in newborn and young lambs. Human pulmonary extraction of PGE<sub>1</sub> is affected by disease state, and is found to be diminished ( $\cong$ 15%) in patients with acute respiratory distress syndrome (ARDS). Pulmonary clearance in such patients varies as a function of both cardiac output and intrinsic clearance. In animals, PGE<sub>1</sub> is also removed from the blood by the liver, kidney and during passage through the upper and lower body extremities.

The major circulating (plasma) metabolite of PGE<sub>1</sub> in humans, rats and dogs is 13,14-dihydro-15-oxoprostaglandin E<sub>1</sub>. The other predominant metabolite observed in rat and dog plasma was 15-oxoprostaglandin E<sub>1</sub>. These two metabolites lack almost complete biological activity. Recently, the formation of a biologically active metabolite, 13,14-dihydro-PGE<sub>1</sub>, has been demonstrated in patients with peripheral arterial occlusive disease and has been shown to lower blood pressure, relax smooth muscle and inhibit platelet aggregation.

*Tissue Distribution.* Autoradiography following administration of PGE<sub>1</sub> in mice and rats indicates that PGE<sub>1</sub> accumulates mainly in the liver and kidneys (highest concentrations), with some distribution in connective tissue and myometrium and least in the CNS. There is very little lung tissue retention of either PGE<sub>1</sub> or its metabolites. The rat liver removes 89-95% of the PGE<sub>1</sub> in a single pass with a significant fraction of the metabolites excreted into the bile. The dog kidney metabolizes about 40% of PGE<sub>1</sub> during a single pass.

*Protein Binding.* PGE<sub>1</sub> is bound primarily to plasma albumin (81%) and to a lesser extent to the  $\alpha$ -globulin IV-4 fraction (55%), although the association is too weak to effect either the rate of metabolism or excretion of PGE<sub>1</sub>. No significant binding could be demonstrated with erythrocytes or white cells.

### Metabolism

The metabolism of PGE<sub>1</sub> in man, rats and guinea pigs involves at least five sets of enzymatic reactions: (a) dehydrogenation of the C-15 hydroxy group, (b) reduction of the 13,14-trans double bond, (c) one or two steps of  $\beta$ -oxidation, (d)  $\omega$ -oxidation, and (e) reduction of the 9-oxo group. In general, considerable similarity exists among animal species in the metabolism of PGE<sub>1</sub>. The corpus cavernosum of the penis possesses significant 15-hydroxyprostaglandin dehydrogenase (PGDH) activity, which may be involved in regulating penile erection through its effect on cavernous tissue prostaglandin concentrations. Local metabolism of intrapenile PGE<sub>1</sub> is indicated by a decline in cavernosal PGE<sub>1</sub> concentrations without an accompanying increase in systemic levels above endogenous levels. In addition, no notable hemodynamic or clinical chemistry changes are noted after intracavernosal injection of PGE<sub>1</sub>.

### Excretion

The main route of elimination of PGE<sub>1</sub> metabolites in humans, dogs, rats and guinea pigs is by the kidney. Urinary excretion of PGE<sub>1</sub> metabolites is rapid and essentially complete within 24 hours. No unchanged PGE<sub>1</sub> has been found in urine. Most of the urinary metabolites are more polar than PGE<sub>1</sub>, thus indicating subsequent metabolism of the two predominant plasma metabolites. The major urinary metabolite of PGE<sub>1</sub> in man, comprising 10-30% of the dose, is 11 $\alpha$ -hydroxy-9,15-dioxo-2,3,4,5-tetranorprosta-1,20 dioic acid. Although only 3 additional human urinary metabolites have been characterized, the disposition of PGE<sub>1</sub> and PGE<sub>2</sub> are similar and metabolites of PGE<sub>1</sub> are considered analogous to those of PGE<sub>2</sub>.

## TOXICOLOGY

<b>Acute Toxicity</b>		
<b>Species</b>	<b>Route</b>	<b>Combined Sex Estimated LD<sub>50</sub> Values, (mg/kg)</b>
Mouse	IV	96 (80-115)
Mouse	IV	76 (66-88)
Mouse Neonate	SC	12 (10-14)
Mouse Adult	SC	76 (63-91)
Mouse	SC	49 (42-56)
Rat	IV	30 (26-34)
Rat	SC	15 (13-17)
Rat Neonate	SC	33 (29-39)
Rat	SC	25 (22-29)
Dog	I-Arterial	Non-toxic at 0.5 mcg/kg/min

Common clinical signs included: depression (inactivity), soft stool or diarrhea and rapid breathing. Hence, alprostadil was found to compromise the CNS, gastrointestinal tract and respiratory system at high doses.

<b>Long-Term Toxicity</b>				
<b>Species</b>	<b>Alprostadil Dose</b>	<b>Route</b>	<b>Duration</b>	<b>Observations</b>
Rat	150, 475, 1500 ng/kg/min	IV	30 d	lethargy, tearing, edema of distal limbs, flushing, enlarged zymbal and mammary glands.
Rat	0.5-2.2 mg/kg/d 1.0-2.5 mg/kg/d	SC	7 d	retarded weight gain, changes in food and water consumption. maximum tolerable dose: 1.0 to 1.5 mg/kg/d (prolonged use)
Dog	32, 100, 320 ng/kg/min	IV	14 d	anorexia, tearing, depressed activity, edema, ptosis of eyelids 8 leukocytes, platelets, alkaline phosphatase, CPK, 9 erythrocytes, Hgb, Hct, calcium, albumin, glucose. treatment-related normocytic anemia.
Dog	25, 80, 250 ng/kg/min	IV	30 d	anorexia, tearing, lethargy, edema, subperiosteal new bone, 8 alkaline phosphatase, fibrinogen, Hct; 9 ALT, AST, BUN, calcium, albumin, glucose, total protein, Hgb, RBC, eosinophil. treatment-related normocytic anemia.
Dog	100 ng/kg/min	IV	30 d	enlarged limb bones, edema, new bone formation, bone resorption and remodelling.
Monkey	0.5, 1.0, 1.5 mg/kg	IM	8 d	emesis, sialorrhoea, depression. maximum tolerable dose: 1 mg/kg (prolonged use)

## Reproduction and Teratology

Alprostadil at doses up to 0.2 mg/kg/day did not adversely affect or alter rat spermatogenesis which is relevant to alprostadil administration to men and represents a 200-fold margin of safety for male reproductive function.

## Mutagenicity

An extensive battery of genetic toxicology studies conducted with alprostadil gave no evidence of mutagenicity or genetic toxicity.

The influence of alprostadil on the growth rate of transplantable tumours was examined in mice receiving continuous intravenous infusion of up to 16 mcg/kg/min alprostadil for 9.5-10 days. Alprostadil treatment had no influence on the growth or malignancy potential of colon or mammary adenocarcinoma.

## Carcinogenicity

No carcinogenicity studies were conducted with alprostadil. The short-term uses and the short biological half-life of alprostadil obviate the need for these studies.

Local Tolerance				
Species	Alprostadil Dose	Route	Duration	Observations
Rat	20, 40, 80 mcg/mL	IV	bolus	concentration dependent pain response.
Monkey	3 mcg/d (20 mcg/mL)	IC <sup>†</sup>	3x/wk, 14 d	raised foci at dose site, mild injection-related foreign body tissue response.
Monkey	9 mcg/dose	IC	3x/wk, 30 d	no penile/non-penile tissue lesions attributable to PGE <sub>1</sub> . raised foci at dose site, mild injection-related foreign body tissue response - reversible.
Monkey	3, 9 mcg/dose	IC	2x/wk, 6 mo	no penile/non-penile tissue lesions attributable to PGE <sub>1</sub> . raised foci, hematomas, sc bleeds at dose site, injection-related foreign tissue response - reversible.
Monkey	3, 8.25 mcg/dose	IC	2x/wk (incl 3-tid doses), 1 yr	no drug-related penile or systemic tissue lesions. penile bruising & reddening, raised foci, injection-related MN and/or PMN leukocyte infiltration, focal fibrous tissue proliferation - reversible.

<sup>†</sup> IC = intracavernosal (intrapenile)

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**PART III: CONSUMER INFORMATION**  
**CAVERJECT STERILE POWDER**  
 (Alprostadil for Injection)

This leaflet is Part III of a three-part "Product Monograph" published when CAVERJECT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CAVERJECT. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**

**What the medication is used for:**

CAVERJECT (Alprostadil for injection) is used:

- In treatment for erectile dysfunction in male adults. Erectile dysfunction is a condition when a man cannot achieve and/or maintain an erection; and
- As an adjunct to diagnostic tests to confirming of erectile dysfunction

CAVERJECT should not be given to patients under 18 years of age. See Warnings and Precautions section of this leaflet.

**What it does:**

CAVERJECT (Alprostadil for injection) relaxes the smooth muscles of the penis. This allows more blood to flow into the penis and helps achieve and/or maintain an erection.

**When it should not be used:**

Do not use CAVERJECT if you have any of the following conditions:

- an allergy to alprostadil or any of the other ingredients in CAVERJECT;
- sickle cell anemia or a history of sickle cell anemia (abnormality of the red blood cells), multiple myeloma (cancer of the bone marrow) or leukemia;
- an erection that lasted more than 4 hours;
- a deformed penis or Peyronie's disease;
- a penile implant;

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

CAVERJECT is not recommended for use in women, newborns and children under 18 years of age.

**What the medicinal ingredient is:**

Alprostadil

**What the nonmedicinal ingredients are:**

Lactose monohydrate, sodium citrate dihydrate, benzyl alcohol, hydrochloric acid and/or sodium hydroxide to adjust the pH.

**What dosage forms it comes in:**

CAVERJECT comes in a vial that contains 20 micrograms (mcg) of alprostadil sterile powder (see details in the "Proper Use of this Medication" section of this leaflet).

**WARNINGS AND PRECAUTIONS**

CAVERJECT may cause prolonged erection (4 to 6 hours) or priapism (over 6 hours).

You should seek immediate medical help for an erection that lasts more than 3 hours.

You must be properly trained by your doctor on how to use CAVERJECT.

CAVERJECT is used with a very thin needle that could break easily. If the needle breaks during use and you can see and touch the broken end, remove it and contact your doctor. If you cannot remove the broken end, seek medical help right away.

If the needle is bent, do not use it and do not try to straighten it before using it. This could make it more likely to break. If the needle is bent, remove it from the syringe, discard it, and attach a new needle to the syringe. See the "Proper Use of this Medication" section of this leaflet.

**CAVERJECT DOES NOT PROTECT against sexually transmitted infections (STIs), including HIV/AIDS. For Protection against STIs, it is advisable to use protective measures.**

**Before or while you use CAVERJECT talk to your doctor if you have any of the following conditions:**

- sickle cell anemia or a history of sickle cell anemia (abnormality of the red blood cells), multiple myeloma (cancer of the bone marrow) or leukemia;
- an erection that lasted more than 4 hours;
- a deformed penis or Peyronie's disease;
- a penile implant;
- blood clotting problems or on medicines to prevent blood clotting such as warfarin or heparin.

CAVERJECT should not be used in children and newborns. CAVERJECT contains benzyl alcohol which can cause death in children, especially in babies born early, and in babies who have a low weight when they are born.

**INTERACTIONS WITH THIS MEDICATION**

Before and while taking CAVERJECT, tell your doctor or pharmacist about all other medications you take including medications that you bought without prescription, vitamins, and natural products.

**PROPER USE OF THIS MEDICATION**

**Usual dose:**

For Erectile Dysfunction:

CAVERJECT is to be injected into either of two areas of the corpora cavernosa (spongy tissue of penis).

CAVERJECT must be given to you first by your doctor in his/her office to determine a dose of CAVERJECT that works for you. This

dose of CAVERJECT should help you achieve and/or maintain an erection not longer than 1 hour. This process is called dosage titration.

When a dose has been selected, your doctor should show you how to safely inject CAVERJECT. And you should also be familiar with the following instructions before giving yourself an injection. If you have any questions, please ask your doctor.

CAVERJECT should be injected not more than once daily and not more than 3 times a week, with at least 24 hours between each dose. Maximum daily dose should not be more than 60 mcg. Do not inject CAVERJECT into an erect penis.

A case of CAVERJECT has enough drug for one injection. The number of cases you need will depend on the length of your therapy.

**CAVERJECT Case Supplies (see Diagram 1)**

CAVERJECT is supplied in boxes that contain five cases. Each case contains the following:

- One vial of CAVERJECT sterile powder in strength of 20 mcg.
- One pre-filled syringe containing bacteriostatic water. This is sterile water containing a preservative and is used to dissolve CAVERJECT. This solution does not contain active drug. You will use this syringe after attaching the needle, to inject the drug into your penis.
- A 27-gauge, 0.5 inch needle. Keep the plastic cover on the needle until ready to inject.
- Two alcohol swabs. It is important to use the swabs to provide hygienic conditions and prevent infection.

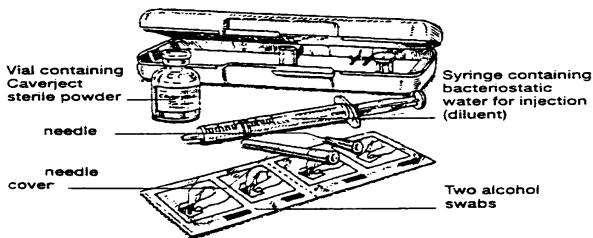


Diagram 1: Vial containing CAVERJECT STERILE POWDER.; Syringe containing bacteriostatic water for injection (diluent); Needle with cover; Two alcohol swabs

**Self-injection Method**

**Preparing the medication**

1. Wash your hands thoroughly with soap and water.
2. Pull back on tabs of needle package to expose open end of needle. Do not let this end touch any surface.
3. Hold syringe tip upwards and remove rubber end cover. Continue to hold syringe upright in one hand. With free hand, pick up needle by covered end.
4. With needle cover still on, attach open end of needle to syringe tip by pushing down and twisting into place (see Diagram 2).

Make sure the needle fits tightly.

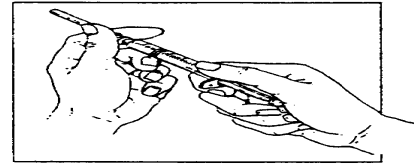


Diagram 2: Joining the needle to the syringe

5. Remove the plastic cap from the vial.
6. Wipe the rubber stopper of the vial, using one of the swabs provided (see Diagram 3). Discard the used swab (the second swab is needed later).

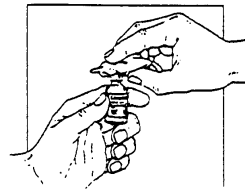


Diagram 3: Wiping the rubber stopper of the vial

7. Handle the syringe by the barrel only. Remove needle cover carefully from the syringe. Do not allow needle to touch any surface.
8. Holding the syringe with needle pointing upward, push plunger to the 1-cc (mL) line marked on the syringe. (This will remove a slight amount of overfill in the syringe.)
9. Pierce needle through the centre portion of the vial's rubber cap. Push down plunger and inject entire contents of syringe (bacteriostatic ( bak-te-reo-stat-ik) water) into the vial. (See Diagram 4)

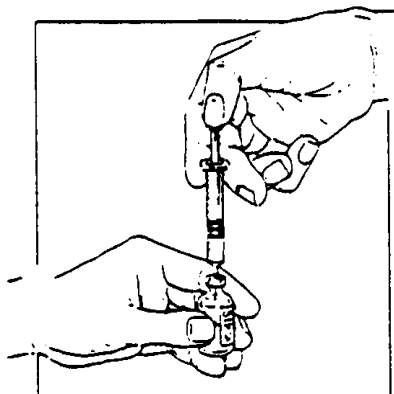
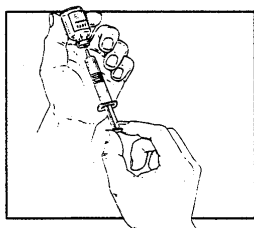


Diagram 4: Injecting bacteriostatic water into the vial

Carefully hold syringe and vial as a unit, and gently swirl the two (do not shake) until the powder dissolves completely. **DO NOT USE** if the resulting solution is cloudy or coloured, or if it contains particles.

**Withdrawing the medication**

1. To withdraw the medication, turn the vial (and syringe) upside down. Keep tip of needle below the level of the fluid. Then slowly withdraw syringe plunger until the amount of solution is level with the line recommended by your doctor (see Diagram 5).



Withdrawing the medication

Diagram 5: Withdrawing the medication

2. If there are air bubbles in the syringe, tap syringe gently to remove them, or inject the solution back into the vial and slowly withdraw again. (See Diagram 6)

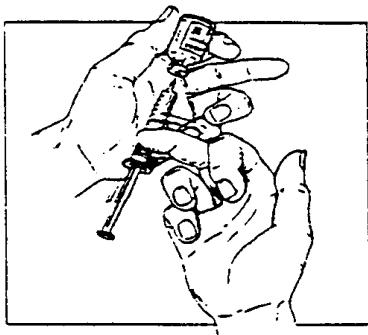


Diagram 6: Tapping the syringe to remove air bubbles

3. Remove needle from bottle and carefully replace needle cover. **DO NOT** puncture the vial more than once, you could contaminate the solution.

Diagram A. Cross-section of penis showing injection sites

Diagram A

Cross-section of the penis showing injection sites

Veins, Arteries, Nerves

Corpora Cavemosa (both)

Injection sites: Needle correctly entering one of the Corpora Cavemosa

Urethra

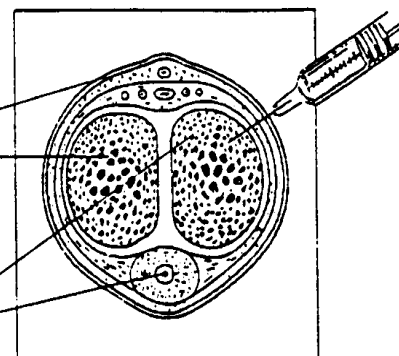
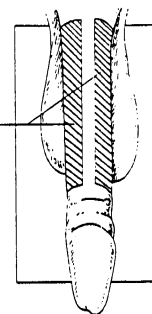


Diagram B. Top view of penis showing injection sites (shaded areas).

Diagram B

Top view of penis showing injection sites

Injection sites



**Self-injecting the medication**

The medication must be injected into either of two areas of the corpora cavernosa (spongy tissue of penis). As you can see from diagrams A and B above, the corpora cavernosa run down both sides of the penis.

Follow these instructions carefully to ensure you inject the medication correctly.

1. Perform the self-injection while sitting in an upright or slightly reclining position and under good lighting.
2. Only use the injection areas shown in diagrams A and B. **DO NOT** inject the very top or underside of your penis. Change the injection site each time you use CAVERJECT. (i.e. choose the right side for this injection, use the left side next time, and so on.) Within either area, the injection point should also be changed each time.
3. Grasp the head of your penis with your thumb and forefinger. Stretch your penis tautly and hold it firmly against your thigh so that it does not slip. In uncircumcised men, the foreskin must be pulled back to assure proper placement of the injection.



- Clean the injection area thoroughly with a new alcohol swab. Put swab to one side; you will need to use it again.
- Hold syringe between thumb and index finger. Do not put your thumb on the plunger. With syringe at a right angle (90E) to your penis, insert needle to penetrate the skin at the injection site. (See Diagram 7) This is a sensitive area, so expect a little discomfort. Avoid any area where veins are clearly visible.

Once the needle pierces the skin and resistance is felt, push needle firmly forward until a distinct "give" is felt and insert the needle all the way in with a steady, continuous motion.

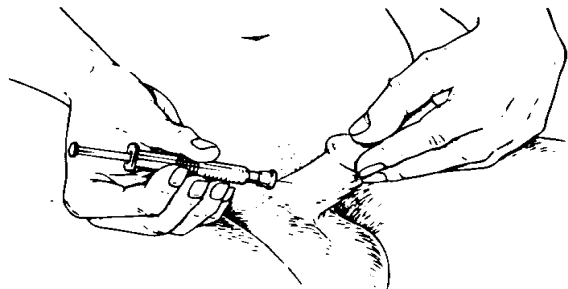


Diagram 7: Inserting the needle into the injection site

- Move your thumb or forefinger to the top of plunger and press down. Inject the entire contents of the syringe using a slow, steady motion. (See Diagram 8)

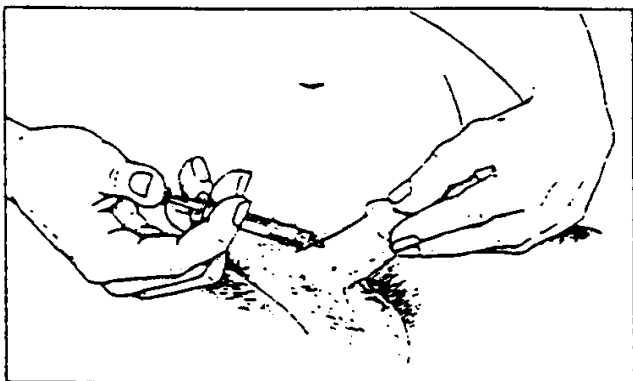


Diagram 8: Injecting the contents of the syringe

- Withdraw the needle from your penis and replace needle cover. Squeeze both sides of your penis immediately, and apply pressure with the alcohol swab to the injection site for about 3 minutes. If bleeding occurs, maintain pressure until the bleeding stops.

As long as you use your doctor's recommended dose, expect an erection to occur within 5 to 20 minutes after an injection.

A standard treatment goal is to produce an erection lasting up to an hour. If an erection is extremely painful (or persists after 3 hours) or if you have other adverse effects that concern you, consult your doctor immediately.

#### Disposal of Used Materials

Always safely dispose of the used syringe (needle), vial and swabs. To help you, the CAVERJECT case is designed as a safe and convenient disposal unit that should be locked. (As another option, your pharmacist may supply a disposal box especially for syringes.)

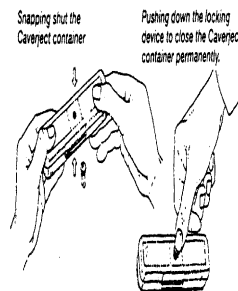


Diagram 9: Snapping shut the CAVERJECT container. Pushing down the locking device to close the CAVERJECT container permanently

- Remove red plastic lock from its holder inside the case. Put this to the side.
- Place used syringe, needle, vial and used swabs in the plastic case. Close firmly so the case snaps shut.
- Remove centre part of CAVERJECT label (perforated area) to show the keyhole.
- To lock case, push the red lock through the hole in the case top. The case is now locked.

**NOTE: ONCE LOCKED, THE CAVERJECT CONTAINER WILL BE PERMANENTLY CLOSED.**

You can now safely dispose of the case. Due to the contents, this is not a recyclable product; **DO NOT** place in a recycle bin.

If you have any questions about the benefits and risks of using CAVERJECT, ask your doctor.

#### **Overdose:**

An erection lasting longer than 3 hours is not a "normal" length of time for the penis to stay rigid. If this occurs, you have probably overdosed. Report this to your doctor immediately. Treat as a medical emergency.

In case of drug overdose, contact your doctor, or a poison control centre, or go to the emergency room of the hospital near you immediately, even if there are no symptoms.

#### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If you have an erection lasting longer than 2 hours, try to reduce the erection using methods suggested by your doctor. Do not wait, it is easier to reduce the erection if you treat it earlier rather than later.

If your penis is still hard after 3 hours see your doctor immediately or go to emergency. Write on a piece of paper the name of the drug, the dose and the time you took it and bring this with you to emergency.

Erections that last more than 6 hours can cause serious and permanent damage.

The most common adverse effect is mild to moderate pain in the penis after injection or during an erection. About one-third of patients experience this effect. Other patients may experience a "burning sensation", "discomfort" or "tension" in the penis.

Occasionally you may have blood blisters (hematoma, ecchymosis) at the site of injection. These relate to improper injection technique rather than the effects of CAVERJECT. If this occurs, ask your doctor to re-instruct you. Pressing down on the injection site will help avoid blood blisters.

Other local adverse effects include: fibrosis (formation of scar tissue in the penile tissues), irritation, sensitivity, penile rash and penile edema (fluid in the tissues).

Rarely occurring are: urgent need to urinate, pain in the testicles or at the base of the penis, erythema (redness of the skin), penile lumps, tenderness, abnormal ejaculation, curved erections, balanitis (inflammation of the tip of the penis) and itching, swelling, inflammation or bleeding at the injection site, urethral bleeding and injuries resulting from poor injection technique.

Rare whole-body effects include: changes in blood pressure, irregular heartbeat, increased pulse rate, dizziness, headache, faintness.

Call your doctor if you notice any of the above or if you experience anything not listed here. Tell your doctor if you have a condition or are taking a medicine that interferes with blood clotting.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
<b>Common</b>	-Prolonged erection			√
	-Pain in the penis after injection or during an erection	√		
	- Burning sensation, discomfort or tension in the penis.	√		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
<b>Uncommon</b>	-Blood blisters (hematoma, ecchymosis) at the site of injection	√		
	-Formation of scar tissue in the penile tissues, irritation, sensitivity, penile rash and fluid in the tissues (penile edema).		√	
<b>Rare</b>	- Pain in the testicles or at the base of the penis		√	
	- Redness of the skin (erythema)	√		
	-Penile lumps	√		
	-Tenderness	√		
	-Abnormal ejaculation	√		
	-Curved erections	√		
	- Inflammation of the tip of the penis (balanitis)	√		
	- Itching	√		
	- Swelling	√		
	-Inflammation or bleeding at the injection site	√		
	- Urethral bleeding		√	
	- Injuries resulting from poor injection technique	√		

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
- Changes in blood pressure - Irregular heartbeat - Increased pulse rate - Dizziness	√		√
- Headache	√		√
- Faintness	√		√
-Broken needle that cannot be removed from penis			√

*This is not a complete list of side effects. For any unexpected effects while taking CAVERJECT, contact your doctor or pharmacist.*

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)  
Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

**NOTE:** Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

**HOW TO STORE IT**

**Storage and handling**

1. You can store unused vials of CAVERJECT Sterile Powder 20 mcg between 2°C to 30°C. Do not freeze.
2. Do not use vials after the expiry date listed on the label.
3. Once dissolved, the CAVERJECT solution must be used immediately. Do not freeze solution.
4. Use contents of each vial only once. Throw out unused solution. See "Disposal of Used Materials" in "Proper Use of this Medication".

**IMPORTANT:** Failure to comply with the following antiseptic measures may lead to infection.

5. To ensure sterile conditions, never contaminate the needle. The disposable needle and syringe require no sterilization steps if the package is intact.
6. **DO NOT** reuse needles or syringes. **DO NOT** give used needles or syringes to others.

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at:  
<http://www.Pfizer.ca>  
or by contacting the Pfizer at:  
1-800-463-6001 (Medical Information)

This leaflet was prepared by Pfizer Canada Inc.

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