PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrCAVERJECT® STERILE POWDER

alprostadil for injection

powder, 20 mcg / vial, intracavernosal

Prostaglandin

Pfizer Canada ULC

17300 Trans-Canada Highway

Kirkland, Quebec H9J 2M5

Date of Initial Authorization:
SEP 16, 2003

Date of Revision:
DEC 20, 2022

Submission Control Number: 264876

RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CAVERJECT STERILE POWDER (alprostadil) is indicated for:

- the intracavernosal treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

Intracavernosal CAVERJECT STERILE POWDER may also be useful as an adjunct to diagnostic tests in the diagnosis of erectile dysfunction.

1.1 Pediatrics

CAVERJECT STERILE POWDER is not indicated for pediatric use (See 2 CONTRAINDICATIONS).

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

CAVERJECT STERILE POWDER (alprostadil) is contraindicated in the following individuals:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients who have any condition that may predispose them to priapism such as sickle cell anemia or trait, multiple myeloma or leukemia.
- Patients with anatomical deformations of the penis, such as angulation, cavernosal fibrosis, Peyronie's disease.
- Patients with penile implants

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

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

4.2 Recommended Dose and Dosage Adjustment

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. During titration no more than two doses should be given within a 24 hour period. 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 4 DOSAGE AND ADMINISTRATION, Dosing Considerations). 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. During titration no more than two doses should be given within a 24 hour period. 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 STERILE POWDER 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 PATIENT MEDICATION INFORMATION).

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 patients 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 STERILE POWDER into an erect penis.

There is no evidence that tolerance to the effects of CAVERJECT STERILE POWDER develops with continued use. The long-term use of CAVERJECT STERILE POWDER 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 STERILE POWDER delivers one dose only. Instructions for proper disposal of the syringe, needle and vial should be followed (see PATIENT MEDICATION INFORMATION).

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 STERILE POWDER.

Adjunct to Laboratory Investigations

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

4.3 Reconstitution

Parenteral Products:

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.

Table – Reconstitution

Parenteral Products (CAVERJECT STERILE POWDER)

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
23.2 mcg	1 mL BWFI	1.13 mL	20 mcg/mL

4.4 Administration

CAVERJECT STERILE POWDER (alprostadil) is administered by direct intracavernosal injection. A 1/2-inch 27- to 30 gauge needle is generally recommended. CAVERJECT STERILE POWDER 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 STERILE POWDER contains benzyl alcohol (see 7 WARNINGS AND PRECAUTIONS).

5 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 LD50 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 STERILE POWDER (alprostadil), overdosage was not observed. If intracavernous overdose of CAVERJECT STERILE POWDER 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 detumesce 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 detumesce 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intracavernosal	Sterile Powder / 20 mcg	Lactose monohydrate, sodium citrate dihydrate, benzyl alcohol, hydrochloric acid and/or sodium hydroxide to adjust the pH

CAVERJECT STERILE POWDER is available in cartons containing 5 cases.

Each case contains: a single dose vial of 20 mcg CAVERJECT STERILE POWDER 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.

7 WARNINGS AND PRECAUTIONS

General

Information to be Provided to Patient

Patients using a self-injection program of therapy should receive proper instruction in both intracavernosal injection and aseptic technique (see PATIENT MEDICATION INFORMATION). Physicians should ensure that patients are able to demonstrate competence and skill with the injection procedure prior to initiating self-injection.

CAVERJECT STERILE POWDER 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.

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 STERILE POWDER, should not increase or decrease their dose without the advice of their physician. Generally, patients should not use CAVERJECT STERILE POWDER more than once a day and not more than 3 times a week, with at least 24 hours between each use.

CAVERJECT STERILE POWDER 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.

Reconstituted vials of CAVERJECT STERILE POWDER which on visual inspection appear cloudy, coloured or contain particulate matter, should be discarded.

Patients who experience an erection lasting longer than 2 hours should attempt to detumesce using methods prescribed by their physician.

Patients should be advised on the possible adverse effects associated with the use of CAVERJECT STERILE POWDER; 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 STERILE POWDER 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.

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 STERILE POWDER.

The use of CAVERJECT STERILE POWDER intracavernosally does not offer any protection from the spread of sexually transmitted diseases. Individuals using CAVERJECT STERILE POWDER should be properly counselled with regards to protective measures to safeguard against the spread of sexually transmitted diseases, including human immunodeficiency virus (HIV) infection.

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 PATIENT MEDICATION INFORMATION).

A patient administration guide, found in every package of CAVERJECT STERILE POWDER, provides a step-by-step method for the proper preparation and administration of CAVERJECT

STERILE POWDER. Patients should be instructed to carefully follow this guide for self-injection.

Carcinogenesis and Mutagenesis

No human data are available. For animal data, see 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Prolonged erection (4 to 6 hours) and/or priapism (>6 hours) are known to occur following intracavernosal administration of vasoactive substances, including CAVERJECT STERILE POWDER (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 5 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 STERILE POWDER should be titrated slowly to the lowest effective dose (see 4 DOSAGE AND ADMINISTRATION).

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

Genitourinary

Underlying treatable medical causes of erectile dysfunction must be diagnosed and treated prior to initiating therapy with CAVERJECT STERILE POWDER (alprostadil).

The results of clinical studies with CAVERJECT STERILE POWDER 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 STERILE POWDER should be discontinued in patients who develop penile angulation, cavernosal fibrosis or Peyronie's disease.

Hematologic

An injection of CAVERJECT STERILE POWDER can induce a small amount of bleeding at the injection site (see 8 ADVERSE REACTIONS). In patients infected with blood-borne diseases, this may increase the transmission of blood-borne diseases between partners.

The safety and efficacy of combinations of CAVERJECT STERILE POWDER and other vasoactive agents have not been systematically studied. Therefore, the use of such combinations is not recommended.

Reproductive Health: Female and Male Potential

- **Fertility**

  CAVERJECT STERILE POWDER is not indicated for use in women (see 2 CONTRAINDICATIONS). Rat reproductive studies indicate that alprostadil at doses of up to 0.2 milligram/kilogram/day (s.c.) (200 times the maximum human recommended dose of 60 microgram) did not have an adverse effect on the reproductive potential of the male rat (see 16 NON-CLINICAL TOXICOLOGY).

- **Function**

  In man, prolonged erection and/or priapism are known to occur following intracavernosal administration of vasoactive substances (see 5 OVERDOSAGE and 7 WARNINGS AND PRECAUTIONS).

- **Teratogenic Risk**

  CAVERJECT STERILE POWDER is not indicated for use in women (see 2 CONTRAINDICATIONS).

Respiratory

The diluent that is used to reconstitute CAVERJECT STERILE POWDER 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.

7.1 Special Populations

7.1.1 Pregnant Women

CAVERJECT STERILE POWDER is not indicated for use in women (see 2 CONTRAINDICATIONS).

7.1.2 Breast-feeding

CAVERJECT STERILE POWDER is not indicated for use in women (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (<18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of CAVERJECT STERILE POWDER in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 2 CONTRAINDICATIONS).

7.1.4 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use (see 2 CONTRAINDICATIONS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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[a]	55	(3)
Injection site hematoma	63	(3)
Penis disorder[b]	46	(3)
Injection site ecchymosis	32	(2)
Penile rash	21	(1)
Penile edema	18	(1)

[a] Includes generalized or deep fibrosis, penile curvature/deviation, and Peyronie's disease.
[b] 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 STERILE POWDER (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 7 WARNINGS AND PRECAUTIONS*)*.

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 4 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[a] by Body System[b] (reported in ≥1% of patients)[c]	**No. (%) of Pts (N=1861)**	
BODY AS A WHOLE	245	(13)
Upper respiratory infection	76	(4)
Flu syndrome	42	(2)
Headache	37	(2)
Trauma[d]	33	(2)
Localized pain[e]	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[f]	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)

[a] number (%) patients reporting the event, with patients reporting the same event more than once counted only once.
[b] number (%) patients reporting a drug-related event within body system, with patients reporting more than one event within the body system counted only once.
[c] no significant adverse events were reported by 294 patients who received 1 to 3 injections of placebo.
[d] includes injuries, fractures, abrasions, lacerations, dislocations.
[e] includes pain in various anatomical structures other than injection site.
[f] 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 STERILE POWDER 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 STERILE POWDER 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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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 PGF2α.

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 PGE1 involve the cardiovascular system, central nervous system (CNS), autonomic nervous system, respiratory system, gastrointestinal system and hematopoietic

system.

10.2 Pharmacodynamics

The actions of PGE1 involve the cardiovascular system, central nervous system (CNS), autonomic nervous system, respiratory system, gastrointestinal system and hematopoietic system.

Cardiovascular: PGE1 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 PGE1 on the cerebral circulation is controversial. Only a low potential exists that intrapenile PGE1 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 PGE1 given by intraventricular injection has sedative effects in animals. The relevance of this pharmacologic activity to peripherally administered PGE1 is questionable since only minute amounts of PGE1 are taken up by the nervous tissue. PGE1 injected into the hypothalamus produces an elevation in body temperature.

Autonomic Nervous System: PGE1 appears to inhibit norepinephrine release from adrenergic nerve endings and inhibits effector responses resulting from adrenergic nerve stimulation.

Cholinergic responses are generally enhanced by PGE1, with the exceptions of the heart and gastric mucosa. PGE1 generally stimulates gastrointestinal smooth muscle and antagonizes sympathomimetic effects on smooth muscle.

Respiratory System: PGE1 inhibits bronchial muscle tone in animals and man when administered by aerosol. Infusion of PGE1 reduces arterial pulmonary pressure in dogs. The actions of PGE1 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 PGE1 from the circulation within minutes.

Gastrointestinal: In rats, guinea pigs, cats and dogs, PGE1 inhibits gastric acid secretion by direct action on the mucosa rather than by effecting mucosal blood flow. In contrast, PGE1 stimulates intestinal secretion. Intra-arterial infusion of PGE1 in dogs (0.01-1 mcg/min) and cats (1 mcg/mL) also decreased jejunal motility. Intra-jejunal PGE1 (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. PGE1 has no effect on salivary secretion in dogs. No consistent effect of PGE1 on insulin secretion is apparent.

Hematopoietic: PGE1 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.

10.3 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 PGE1 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 PGE1 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-PGE1 increased, reaching a peak at 30 minutes and falling to pre-dose levels by 60 minutes post injection.

Elimination

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 PGE1 or its metabolites after an intravenous administration.

Special Populations and Conditions

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%).

- **Pediatrics** CAVERJECT STERILE POWDER contains the diluent benzyl alcohol and is contraindicated in children and newborns (see 2 CONTRAINDICATIONS).

  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.

- **Geriatrics** The potential effect of age on the pharmacokinetics of alprostadil has not been formally evaluated. In patients with 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).
- **Sex** 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.
- **Ethnic Origin** The influence of race on the pharmacokinetics of alprostadil has not been formally studied.
- **Hepatic Insufficiency** The effects of 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 hepatic function will have a major influence on the pharmacokinetics of alprostadil.
- **Renal Insufficiency** The effects of renal 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 function will have a major influence on the pharmacokinetics of alprostadil.

11 STORAGE, STABILITY AND DISPOSAL

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

Reconstituted Solutions 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.

12 SPECIAL HANDLING INSTRUCTIONS

Always safely dispose of the used syringe (needle), vial and swabs. To help you, the CAVERJECT STERILE POWDER 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.)

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

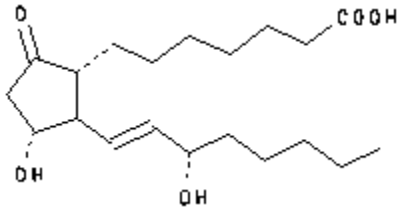
Drug Substance

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

Chemical name: (11α, 13E, 15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid.

Molecular formula and molecular mass: $C_{20}H_{34}O_5$; 354.49

Structural formula:



Physicochemical properties:

- an odourless, white to off-white crystalline powder.
- melting point of 115° to 116°C.
- acid dissociation constant (Ka) is 1.1 x 10-5
- solubility is 80 mcg/mL in water at 35°C.
- pH of 5.15 with 52 mcg /mL alprostadil in deaerated water at 23°C.
- partition coefficient of 0.7 in soyabean oil/water.

Product Characteristics:

CAVERJECT STERILE POWDER

STERILE POWDER Ingredients	20 mcg Vial	
	Dry Powder (per vial)	Reconstituted (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	-

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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The information on the trial design and study demographics on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity		
Species	**Route**	**Combined Sex Estimated LD_{50} Values, (mg/kg)**
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.

Long-Term Toxicity				
Species	**Alprostadil Dose**	**Route**	**Duration**	**Observations**
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, sialorrhea, depression. maximum tolerable dose: 1 mg/kg (prolonged use)

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[†]	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_1. 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_1. 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.

[†] IC = intracavernosal (intrapenile)

Genotoxicity: 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.

Reproductive and Developmental Toxicology: Rat reproductive studies indicate that alprostadil at doses of up to 0.2 milligram/kilogram/day (s.c.) (200 times the maximum human recommended dose of 60 microgram) did not have an adverse effect on the reproductive potential of the male rat.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]CAVERJECT® STERILE POWDER

alprostadil for injection

Read this carefully before you start using **CAVERJECT STERILE POWDER** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CAVERJECT STREILE POWDER**.

What is CAVERJECT STERILE POWDER used for?

CAVERJECT STERILE POWDER is used in adult males:

- in the treatment of erectile dysfunction. Erectile dysfunction is a condition when a man cannot achieve and/or maintain an erection.
- together with diagnostic tests to confirm erectile dysfunction

How does CAVERJECT STERILE POWDER work?

CAVERJECT STERILE POWDER relaxes the smooth muscles of the penis. This allows more blood to flow into the penis and helps to achieve and/or maintain an erection.

What are the ingredients in CAVERJECT STERILE POWDER?

Medicinal ingredients: alprostadil

Non-medicinal ingredients: benzyl alcohol, hydrochloric acid and/or sodium hydroxide to adjust the pH, lactose monohydrate, sodium citrate dihydrate

CAVERJECT STERILE POWDER comes in the following dosage forms:

Sterile powder: 20 mcg / vial

Do not use CAVERJECT STERILE POWDER if:

- you are allergic to alprostadil or any of the non-medicinal ingredients (see **What are the ingredients in CAVERJECT STERILE POWDER?**)
- you have sickle cell anemia or a family history of sickle cell anemia (abnormality of the red blood cells), multiple myeloma (cancer of the bone marrow) or leukemia (cancer of the blood)
- you have an erection that has lasted more than 4 hours
- you have a deformed penis or Peyronie's disease (a condition that causes the penis to curve)
- you have a penile implant
- you have been told you should not be sexually active
- you are a woman or are under the age of 18

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use CAVERJECT STERILE POWDER. Talk about any health conditions or problems you may have, including if you:

- have blood clotting problems or take medicines to prevent blood clotting such as warfarin or heparin
- have a disease that is carried in your blood. You could transmit this disease to your partner as there can be a small amount of bleeding where you inject CAVERJECT STERILE POWDER.

Other warnings you should know about:

You must be properly trained by your healthcare professional before you begin to self-inject CAVERJECT STERILE POWDER.

Prolonged erection: CAVERJECT STERILE POWDER may cause prolonged erection (4 to 6 hours) or priapism (over 6 hours):

- If you have an erection lasting longer than 2 hours, try to reduce the erection using the methods suggested by your healthcare professional. 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 get immediate medical help. Write down the name of the medicine, the dose and the time you took it and bring this with you to the emergency room.
- Erections that last more than 6 hours can cause serious and permanent damage.

Injection site problems: Occasionally you may have problems at the injection site such as swelling, inflammation, bruising or bleeding or blood blisters. These are usually related to improper injection technique. If this happens, ask your healthcare professional to go over the self-injection techniques with you again.

Broken or bent needle: CAVERJECT STERILE POWDER 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 talk to your healthcare professional immediately after. If you cannot remove the broken end, get immediate medical help.

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. Remove it from the syringe, discard it, and attach a new needle to the syringe. See **How to use CAVERJECT STERILE POWDER**, below.

Sexually Transmitted Infections (STIs): CAVERJECT STERILE POWDER does NOT protect against STIs, including HIV/AIDS. For protection against STIs, use protective measures when having oral or penetrative sex, such as condoms.

Use in children: CAVERJECT STERILE POWDER is not to be used in children and newborns. It 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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CAVERJECT STERILE POWDER:

- anticoagulants, medicines used to prevent blood clotting, such as warfarin or heparin. You may be more likely to bleed after injecting CAVERJECT STERILE POWDER.

How to use CAVERJECT STERILE POWDER:

- CAVERJECT STERILE POWDER is to be injected into either of the two areas of the corpora cavernosa (spongy tissue of penis).
- CAVERJECT STERILE POWDER must be given to you first by your healthcare professional in their office to determine a dose that works for you. This dose should help you achieve and/or maintain an erection not longer than 1 hour. This process is called dosage titration.
- When your dose has been selected, your healthcare professional will show you how to safely inject CAVERJECT STERILE POWDER. The instructions are provided below. Make sure you are familiar with the instructions before giving yourself an injection. If you have any questions, talk to your healthcare professional.
- Do NOT change your dose without talking to your healthcare professional.
- Do NOT inject CAVERJECT STERILE POWDER into an erect penis.
- DO NOT reuse needles or syringes. DO NOT give used needles or syringes to others.

Usual dose:

- CAVERJECT STERILE POWDER should not be used more than once daily or more than 3 times a week.
- You must wait at least 24 hours between each dose.
- The maximum daily dose should not be more than 60 mcg.

CAVERJECT STERILE POWDER case supplies (see Diagram 1):

CAVERJECT STERILE POWDER is supplied in boxes that contain five cases. One case has enough medicine for one injection. Each case contains the following:

- One 20 mcg vial of CAVERJECT STERILE POWDER.
- One pre-filled syringe containing bacteriostatic (bak-te-reo-stat-tik) water for injection. This is sterile water containing a preservative. It is used to dissolve CAVERJECT STERILE POWDER. This solution does not contain any medicinal ingredients. You will use this syringe after attaching the needle, to inject the prepared medicine 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 make sure the injection site is clean to prevent infection.

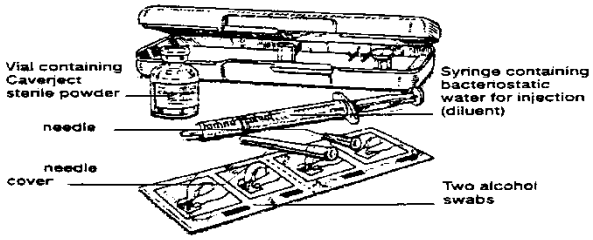


Diagram 1: Vial containing 20 mcg CAVERJECT STERILE POWDER.; Syringe containing bacteriostatic water for injection; Needle with cover; Two alcohol swabs

Instructions for self-injection of CAVERJECT STERILE POWDER

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 the syringe upright in one hand. With your free hand, pick up needle by covered end.
4. With the needle cover still on, attach the open end of the needle to the syringe tip by pushing down and twisting into place (see **Diagram 2**). Make sure the needle fits tightly.

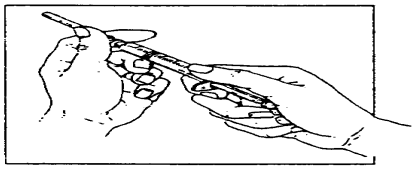


Diagram 2: Joining the needle to the syringe.

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).

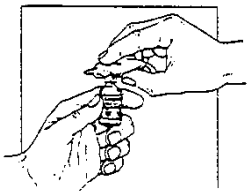


Diagram 3: Wiping the rubber stopper of the vial.

7. Handle the syringe by the barrel only. Remove the needle cover carefully from the syringe. Do not allow the needle to touch any surface.
8. Holding the syringe with the 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 the needle through the center portion of the vial's rubber cap. Push down the

plunger and inject the entire contents of the syringe (bacteriostatic water) into the vial (see **Diagram 4**).

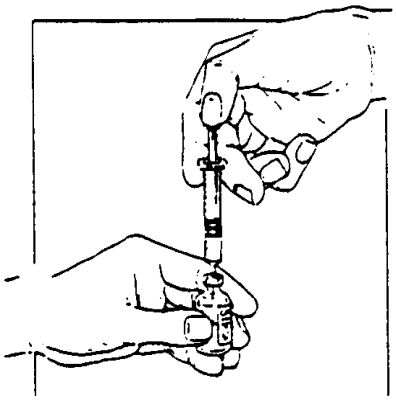


Diagram 4: Injecting bacteriostatic water into the vial.

10. Carefully hold the syringe and the 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 the tip of the needle below the level of the fluid. Then slowly withdraw the syringe plunger until the amount of solution is level with the line recommended by your healthcare professional (see **Diagram 5**).

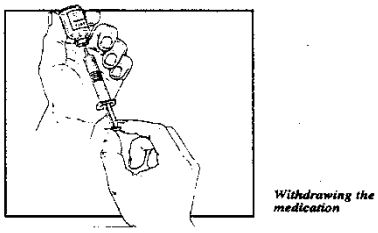


Diagram 5: Withdrawing the medication.

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

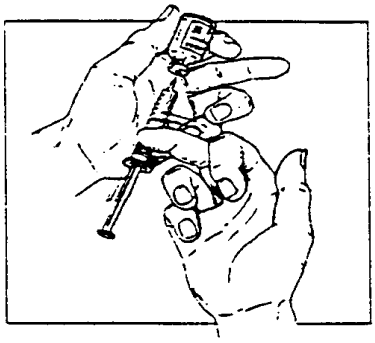


Diagram 6: Tapping the syringe to remove air bubbles.

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

Diagram A. Cross-section of penis showing injection sites.

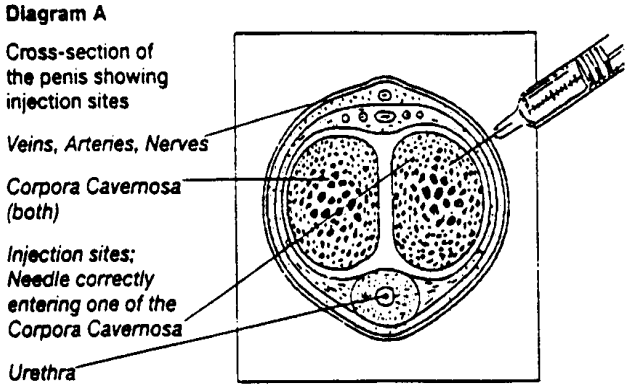
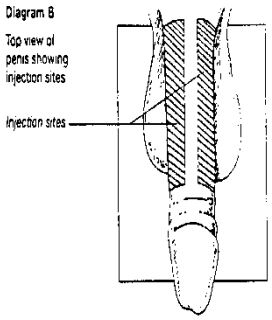


Diagram B. Top view of penis showing injection sites (shaded areas).



Self-injecting the medication:

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

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 **Diagram A** and **Diagram B**. DO NOT inject the very top or underside of your penis. Change the injection site each time you use CAVERJECT STERILE INJECTION (i.e. choose the right side for this injection, use the left side next time, and so on).
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.
4. Clean the injection area thoroughly with a new alcohol swab. Put the swab to one side; you will need to use it again.
5. Hold the syringe between your thumb and index finger. Do not put your thumb on the plunger. With the syringe at a right angle (90°) to your penis, insert the 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.
6. Once the needle pierces the skin and resistance is felt, push the needle firmly forward until a distinct "give" is felt and insert the needle all the way in with a steady, continuous motion.

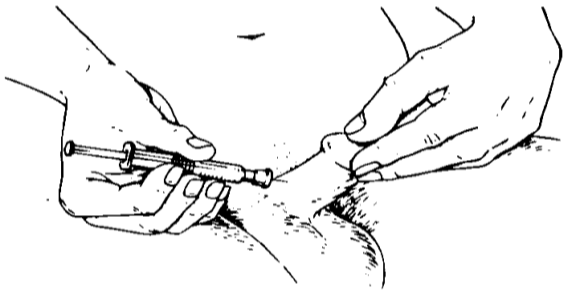


Diagram 7: Inserting the needle into the injection site.

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

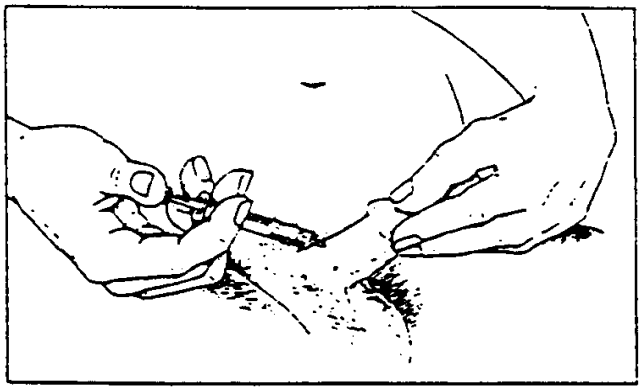


Diagram 8: Injecting the contents of the syringe.

8. Withdraw the needle from your penis and replace the 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 healthcare professional'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 side effects that concern you, talk to your healthcare professional immediately.

Disposal of used materials:

Always safely dispose of the used syringe (needle), vial and swabs. To help you, the CAVERJECT STERILE POWDER 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.

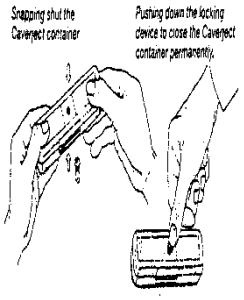


Diagram 9: Snapping shut the CAVERJECTSTERILE POWDER case. Pushing down the locking device to close the CAVERJECT STERILE POWDER case permanently.

1. Remove the red plastic lock from its holder inside the case. Put this to the side.
2. Place the used syringe, needle, vial and used swabs in the plastic case. Close firmly so the case snaps shut.

3. Remove the center part of CAVERJECT STERILE POWDER label (perforated area) to show the keyhole.
4. To lock the case, push the red lock through the hole in the case top. The case is now locked.

NOTE: ONCE LOCKED, THE CAVERJECT STERILE POWDER 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.

Overdose:

If you think you, or a person you are caring for, have used too much CAVERJECT STERILE POWDER, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

An erection lasting longer than 3 hours means you have probably used too much CAVERJECT STERILE POWDER. If this happens get immediate medical help.

What are possible side effects from using CAVERJECT STERILE POWDER?

These are not all the possible side effects you may have when using CAVERJECT STERILE POWDER. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- mild to moderate pain in the penis after injection or during an erection
- burning sensation, discomfort or tension in the penis
- irritation, sensitivity, tenderness, numbness
- penile rash, redness
- headache
- dizziness, faintness
- urgent need to urinate

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Prolonged erection: long-lasting (greater than 3 hours in duration) and painful erection of the penis			**√**
UNCOMMON			
Fibrosis (formation of scar tissue in the penile tissues): penile lumps, can cause curvature of the penis or		**√**	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
curved, painful erections (Peyronie's disease)			
Penile edema: painless, non-tender swelling of the penis		**√**	
RARE			
Pain in the testicles or at the base of the penis		**√**	
Abnormal ejaculation	**√**		
Balanitis: inflammation of the tip of the penis, itching	**√**		
Injection site problems (injuries resulting from poor injection technique): swelling, inflammation, bruising or bleeding at the injection site, bleeding from the urethra, blood blisters, itching			**√**
Changes in blood pressure: **Low:** dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up) **High:** shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		**√**	
Heart problems: fast or irregular heartbeat		**√**	
Broken needle: needle that cannot be removed from penis			**√**
Phimosis (inability to retract the foreskin covering the head of the penis): tight ring or band of foreskin around the tip of the penis preventing retraction		**√**	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

1. Store unused vials of CAVERJECT STERILE POWDER between 2°C to 30°C. Do not freeze.
2. Do not use the vials after the expiry date listed on the label.
3. Once dissolved, the solution must be used immediately. Do not freeze the solution.
4. Use the contents of each vial only once. Throw out any unused solution (See **Disposal of used materials** under **How to use CAVERJECT STERILE POWDER**).
5. Keep out of reach and sight of children.

If you want more information about CAVERJECT STERILE POWDER:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.

Last Revised: DEC 20, 2022