1. NAME OF THE MEDICINAL PRODUCT

CAVERJECT®
(ALPROSTADIL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each powder vial contains:
- Alprostadil 20 µg
- Lactose monohydrate
- Sodium citrate
- α-cyclodextrine
- 10% Hydrochloric acid
- 10% Sodium hydroxide

Each diluent syringe (1 ml) contains:
- Benzyl alcohol 9 mg
- Water for injection

3. PHARMACEUTICAL FORM

Pharmaceutical form after reconstitution: Injectable solution.

Way of administration: Intracavernosal.

Packages: Vial with 20 µg alprostadil + pre-filled syringe with 1 ml bacteriostatic water for injection + 2 needles (22G1½ and 30G½).

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Intracavernosal alprostadil (CAVERJECT®) is indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

Intracavernosal alprostadil (CAVERJECT®) may be a useful adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

CAVERJECT® is not indicated for pediatric use (see Section 4.4 Special Warnings and Precautions for Use, Benzyl alcohol).

4.2 Posology & Method of Administration

CAVERJECT® is administered by direct intracavernosal injection. A 1/2-inch, 27- to 30-gauge needle is generally recommended.

The dose of CAVERJECT® should be individualized for each patient by careful titration under supervision by the physician. In clinical studies, patients were treated with CAVERJECT® in doses ranging from 0.2 to 140 µg; however, since 99% of patients received

doses of 60 µg or less, doses of greater than 60 µg are not recommended. In general, the lowest possible effective dose should always be employed.

INITIAL TITRATION IN PHYSICIAN'S OFFICE

The following titration schedule should be followed, depending on erectile response, until the dose that produces an erection suitable for intercourse and not exceeding a duration of 60 minutes is reached. If there is no response to the administered dose, 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 1-day interval before the next dose is given. The patient must stay in the physician's office until complete detumescence occurs.

	Neurogenic etiology (spinal cord injury)	**Vasculogenic, psychogenic, or mixed etiology**
Starting dose to inject	1.25 µg	2.5 µg
Second dose to inject	2.5 µg	Partial response: 5.0 µg No response: 7.5 µg
Third dose to inject	5.0 µg	
Additional increments increases until optimal dose is achieved	5.0 µg	5.0-10.0 µg

MAINTENANCE THERAPY

The first injections of CAVERJECT® must be done at the physician's office by medically trained personnel.

Self-injection therapy by the patient can be started only after the patient is properly instructed and well trained in the self-injection technique. The physician should make a careful assessment of the patient's skills and competence with this procedure. The intracavernosal injection must be done under sterile conditions. The site of injection is usually along the dorso-lateral aspect of the proximal third of the penis. Visible veins should be avoided. The side of the penis that is injected and the site of injection must be alternated; the injection site must be cleansed with an alcohol swab. Self-injection therapy for use at home should be initiated at the dose that was determined in the physician's office. The dose that is selected for self-injection treatment should provide the patient with an erection that is satisfactory for sexual intercourse, and maintained for no longer than 60 minutes. If the duration of erection is longer than 60 minutes the dose should be reduced. Careful and continuous follow-up of the patient while in the self-injection program must be exercised. This is especially true for the initial self-injections, since adjustments in the CAVERJECT® dose may be needed. Dose adjustment, if required, should be made only after consultation with the physician, and should be adjusted in accordance with the titration guidelines described above. (Up to 57% of patients in one clinical study required dose adjustment). While on self-injection treatment, it is recommended that the patient visits the prescribing physician's office every 3 months. At that time, the efficacy and safety of the therapy should be assessed, and the dose of CAVERJECT® should be adjusted, if needed. The recommended frequency of injection is no more than once daily and no more than three times weekly. The reconstituted vial of CAVERJECT® is intended for single use only and should be discarded after use. The user should be instructed in the proper disposal of the syringe, needle, and vial.

Once reconstituted, no additional materials should be injected into the vial. When stored in the original container, the reconstituted CAVERJECT® solution is physically, chemically, and microbiologically stable for a period of 24 hours at room temperature. The product should be inspected visually for particulate matter and discoloration prior to administration. Do not freeze reconstituted solutions.

CAVERJECT® AS AN ADJUNCT TO THE DIAGNOSIS OF ERECTILE DYSFUNCTION

In the simplest diagnostic test for erectile dysfunction (pharmacologic testing), patients are monitored for the occurrence of an erection after an intracavernosal injection of CAVERJECT®.

Extensions of this testing are the use of CAVERJECT® as an adjunct to laboratory investigations, such as duplex or Doppler imaging, ^{133}Xenon washout tests, radioisotope penogram, and penile arteriography, to allow visualization and assessment of penile vasculature. For any of these tests, a single dose of CAVERJECT® that induces an erection with firm rigidity should be used.

DILUTION AND SELF-INJECTION PROCEDURE USING THE PRE-FILLED DILUENT SYRINGE WITH DETACHED NEEDLE

This guide is not meant to substitute for the advice and counsel of your doctor.

1. Check your pack

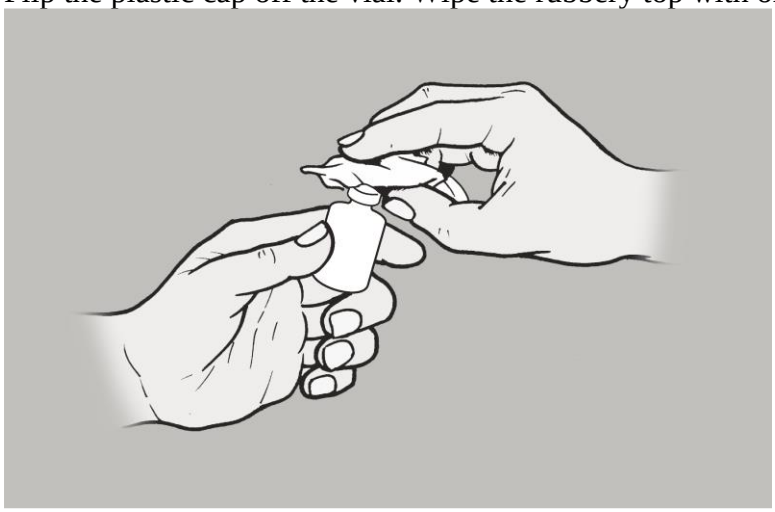
Make sure that the vial is the correct strength and the expiry date is still valid. The vial, syringe and needles all have protective covers. The flip-off cap on the vial can rotate; this is normal.

Check that all the covers are on firmly and if they are not on properly, do not use them – take the whole pack back to your pharmacist. There are two needles in the pack:

- The larger 22 gauge needle with the grey end is used to mix the solution and CAVERJECT® Powder.
- The smaller and finer 30 gauge needle with the yellow end is used to inject the mixture into your penis.

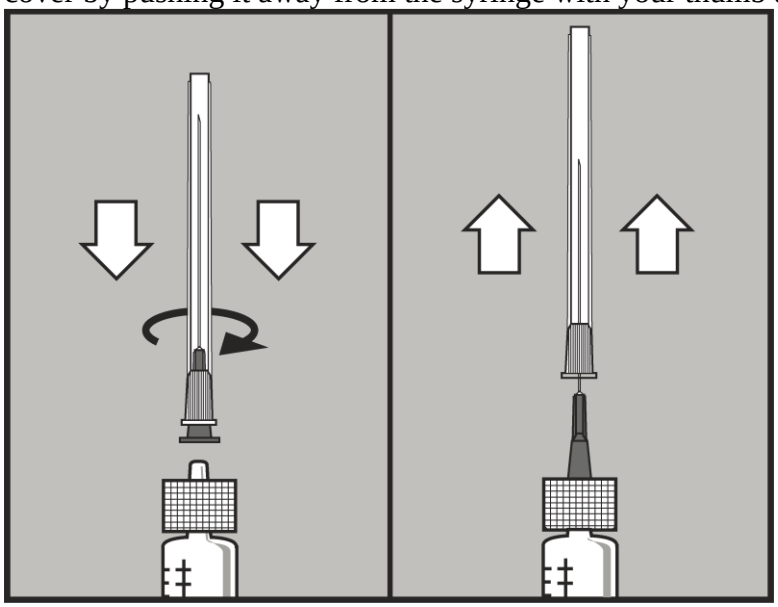
2. To prepare the vial

Flip the plastic cap off the vial. Wipe the rubbery top with one of the wet antiseptic pads.



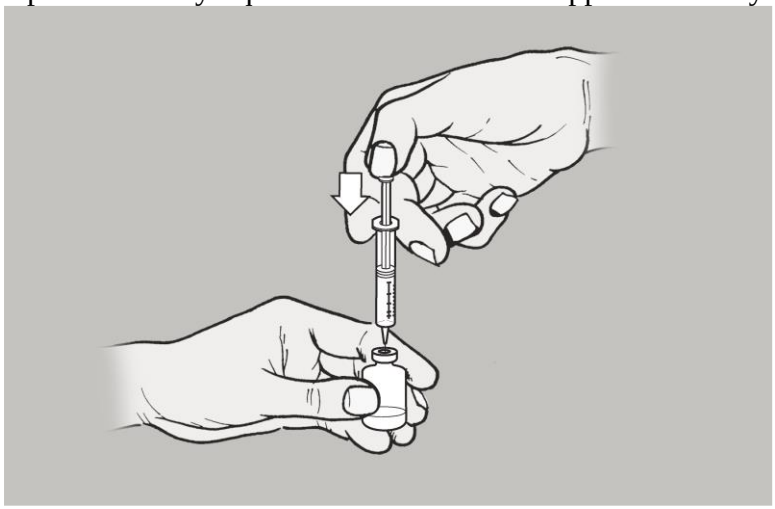
3. Fitting the needle to the syringe

Hold the syringe and twist the white tamper evident cap to break the seal. Take the foil off the larger needle, (22 gauge) with the grey end, keeping the cover on. Join the needle to the syringe by turning the needle clockwise tightly onto the syringe, then remove the needle cover by pushing it away from the syringe with your thumb and forefinger.



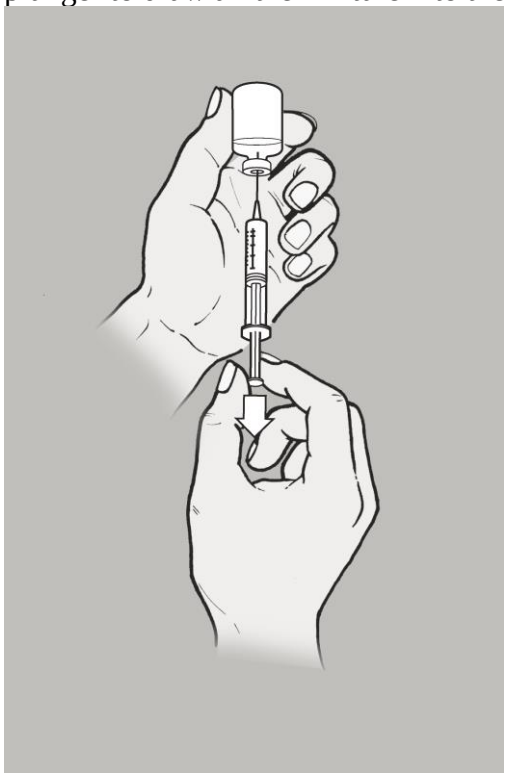
4. Mixing the solution with the powder

Push the needle through the rubbery middle of the vial top. Press the plunger down firmly to squirt all the solution onto the powder. Gently swirl the vial until all the powder has dissolved. If the mixture is cloudy or does not dissolve completely, do not use it. Never use tap water or any liquid other than the one supplied in the syringe.



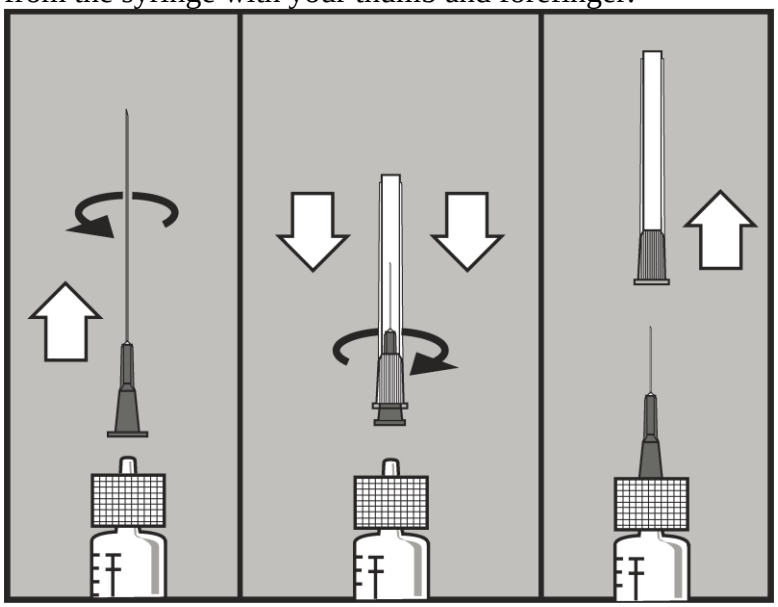
5. Filling the syringe

With the needle still inserted, turn the vial upside down. The needle should support the vial unaided. Make sure the needle tip is underneath the level of the liquid. Gently pull the plunger to draw all the mixture into the syringe. Pull the needle out of the vial.



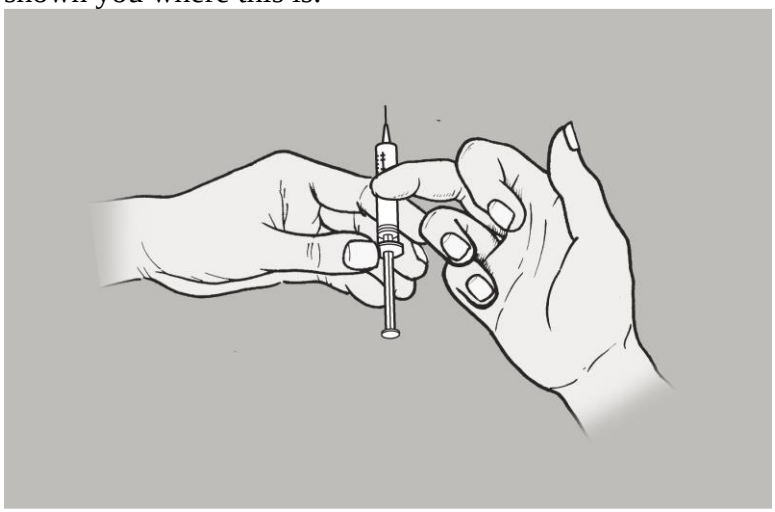
6. Changing to the injecting needle

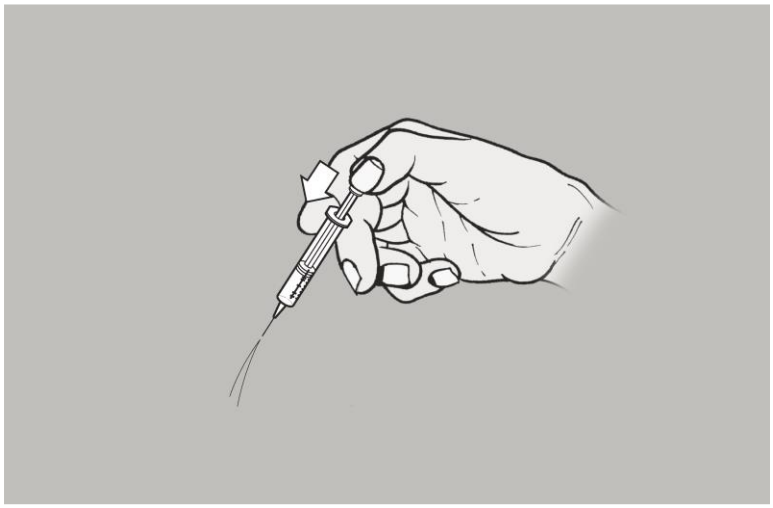
Gently twist the larger needle anticlockwise off the syringe. Remove the smaller injecting needle, (30 gauge) with the yellow end from its package, keeping the cover on. Twist the needle clockwise tightly onto the syringe, then remove the needle cover by pushing it away from the syringe with your thumb and forefinger.



7. Setting the dose

Tap the syringe gently to send any air bubbles to the top, then push the plunger to squeeze the air bubbles out, ensuring that at least one drop of solution comes out of the needle. Continue pushing until the plunger is exactly at the right mark for your dose. Your doctor will have shown you where this is.



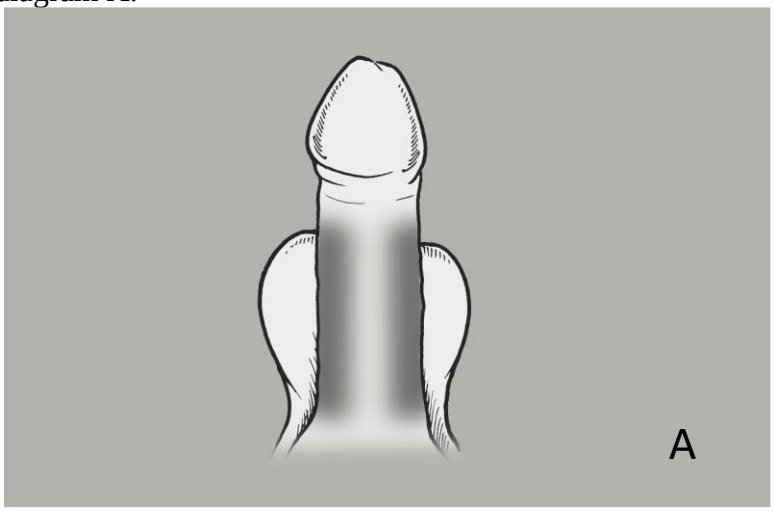


How do you do the injection?

- Get undressed and make yourself comfortable. Take some time to relax yourself. If your prescriber has recommended use of the second antiseptic pad, open it now.

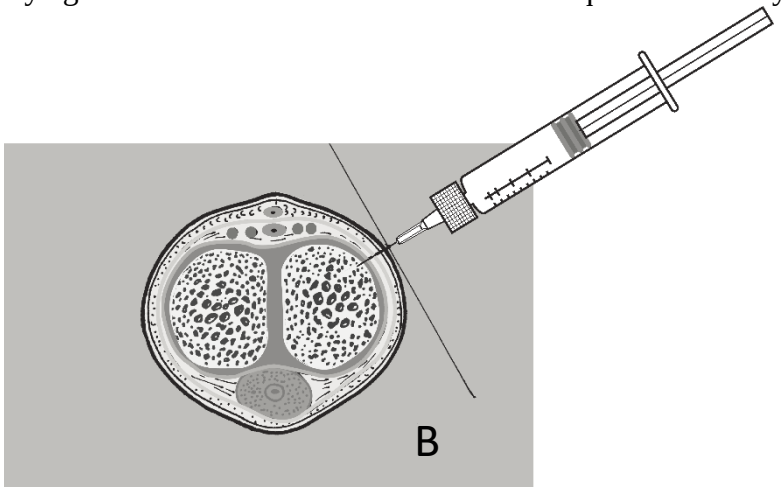
- Make sure that the injection needle is **not** bent. If it is, **do not** use it and throw it away. **Do not** attempt to straighten it out.

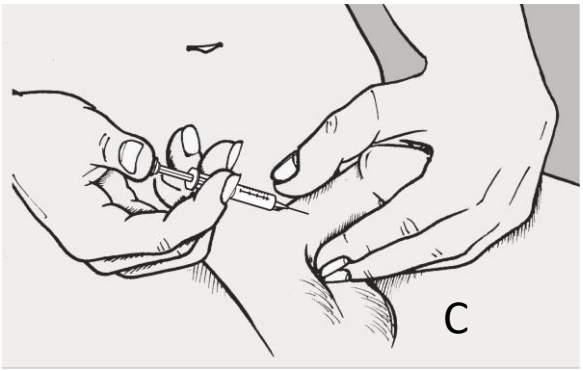
- Take hold of the penis from the front, with the first two fingers underneath close to the testicles and the thumb on top. Gently squeeze the penis between your thumb and finger so that the injection site bulges out. If there is a foreskin on the penis, make sure it is stretched. The injection will go into the part of the penis shown as the shaded area in diagram A.



- If recommended by your prescriber wipe the skin over this area with the second pad and let it dry.

- Keeping a firm grip on the penis and taking the syringe in your free hand, push the needle straight through the skin all the way into the bulgy part avoiding veins or other obvious blood vessels. The angle is shown in diagrams B and C. Push the plunger firmly and if the CAVERJECT® does not come out fairly easily, move the needle slightly and try again. **Do not** force the CAVERJECT® liquid from the syringe.





- Pull the needle out. On the needle mark, press gently with the pad or your thumb, as recommended by your prescriber. Massage the penis to help the CAVERJECT® spread through it.

- Do not keep any mixture in the syringe to use for a second injection.

After using the contents of this pack, dispose of all materials safely.

Your pharmacist may be able to supply a disposal box especially for syringes.

4.3 Contraindications

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

Patients with penile implants should not be treated with CAVERJECT®.

CAVERJECT® 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.

4.4 Special Warnings and Precautions for Use

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

Priapism
Priapism (erection lasting over 6 hours) is known to occur following intracavernosal administration of vasoactive substances, including CAVERJECT®. The patient should be instructed to immediately report to his physician any erection that persists for longer than 6 hours. Treatment of priapism should be according to established medical practice.

Penile fibrosis
Penile fibrosis, including Peyronie's disease, occurred in 1% of patients in clinical studies with CAVERJECT®. 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.

Sexually transmitted and blood borne diseases, including human immunodeficiency virus (HIV)
Use of CAVERJECT® offers no protection from the transmission of sexually transmitted diseases. Because a small amount of bleeding may occur at the injection site, individuals who use CAVERJECT® should be counselled about the protective measures that are necessary to guard against the spread of sexually transmitted diseases, including the HIV, and blood-borne diseases.

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

Benzyl alcohol
The preservative benzyl alcohol 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.

Needle breakage
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.

4.5 Interaction with Other Medicinal Product and Other Forms of Interactions

No known interactions. CAVERJECT® is not intended for co-administration with any other agent for the treatment of erectile dysfunction.

4.6 Fertility, Pregnancy and Lactation

Not applicable

4.7 Effects on Ability to Drive and Use Machines

Not applicable

4.8 Undesirable Effects

The following adverse reactions information was obtained from clinical studies sponsored by Pharmacia & Upjohn involving 1,712 patients treated with CAVERJECT®.

The most frequent adverse reaction after intracavernosal injection of CAVERJECT® is penile pain. In studies, 34% of the patients reported penile pain at least once, however, this event was associated with only 11% of the administered injections. In the majority of the cases, penile pain was rated mild or moderate in intensity. Three percent of patients discontinued treatment because of penile pain.

Hematoma at the site of injection, which is related to the injection technique rather than to the effects of alprostadil, occurs in 3% of patients.

The frequency of prolonged erection (defined as an erection that lasts for 4 to 6 hours) was 2%.

The frequency of priapism (defined as an erection that lasts 6 hours or longer) was 0.5%. In the majority of cases, spontaneous detumescence occurred.

The following local adverse reactions occurred in 1.0%-1.5% of patients: injection site ecchymosis, penile rash, penile edema, and penile fibrosis. The following local adverse reactions were reported by 1% or fewer of patients: balanitis, injection site hemorrhage, injection site inflammation, injection site pruritus, injection site swelling, urethral bleeding, penile warmth, numbness, yeast infection, irritation, decreased sensitivity, phimosis, erythema, venous leak, painful erection, and abnormal ejaculation.

In terms of systemic events, the following were reported for fewer than 1% of patients in clinical studies, and were judged to be possibly related to CAVERJECT® use: testicular pain, testicular swelling, scrotal erythema, pain or tightness, urinary frequency, urinary urgency, impaired urination, hypotension, vasodilatation, hypertension, supraventricular extrasystole, peripheral vascular disorder, dizziness, hypoesthesia, buttock weakness, localized pain (buttocks pain, leg pain, genital pain, abdominal pain), headache, pelvic pain, back pain, flu syndrome.

Hemodynamic changes, manifested as decreases in blood pressure and increases in pulse rate, were observed during clinical studies, principally at doses above 20 µg and above 30 µg of CAVERJECT®, respectively, and appeared to be dose-dependent. However, these changes were usually clinically unimportant; only three patients (0.2%) discontinued the treatment because of symptomatic hypotension.

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

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC.

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**
Infections and infestations			Yeast infection

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100
Nervous system disorders			Vasovagal reaction, hypoesthesia (systemic), penile numbness, decreased penile sensitivity
Eye disorders			Mydriasis
Cardiac disorders			Supraventricular extrasystoles
Vascular disorders			Hypotension, vasodilatation, peripheral vascular disorder, penile venous leak
Gastrointestinal disorders			Nausea, dry mouth
Skin and subcutaneous tissue disorders		Erythema	Rash, diaphoresis, pruritus
Musculoskeletal, connective tissue and bone disorders			Leg cramps
Renal and urinary disorders			Urethral bleeding, hematuria, urination impaired, urinary frequency, urinary urgency
Reproductive system and breast disorders	Penile pain	Penile fibrosis including Peyronie's disease, angulation, and fibrotic nodules, erection prolonged	Priapism, pelvic pain, painful erection, testicular pain, scrotal disorder, penile irritation, balanitis, scrotal edema, penile warmth, testicular disorder, ejaculation abnormal
Congenital, familial and genetic disorders			Phimosis
General disorders and administration site conditions		Injection site hematoma, injection site ecchymosis	Injection site hemorrhage, injection site inflammation, injection site edema, injection site swelling, localized muscle weakness, injection site pruritus
Investigations			Blood creatinine increased

4.9 Overdose

In man, prolonged erection and/or priapism are known to occur following intracavernosal administration of vasoactive substances, including alprostadil. The treatment of priapism may include different approaches such as aspiration, intracavernosal injection of sympathomimetic amines or surgery. Patients should be instructed to report to a physician any erection lasting for a prolonged time period, such as 6 hours or longer.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Alprostadil is present in various mammalian tissues and fluids. It has a diverse pharmacologic profile, among which some of its more important effects are vasodilation, inhibition of platelet aggregation, inhibition of gastric secretion, and stimulation of intestinal and uterine smooth muscle. The pharmacologic effect of alprostadil in the treatment of erectile dysfunction is presumed to be mediated by inhibition of alpha$_1$-adrenergic activity in penile tissue and by its relaxing effect on cavernosal smooth muscle.

5.2 Pharmacokinetics Properties

The pharmacokinetics of intravenously administered alprostadil have been extensively studied. When administered intravenously to man, alprostadil is rapidly transformed to relatively inactive metabolites. In healthy men, 70% to 90% of alprostadil is extensively extracted and metabolized in a single pass through the lungs, resulting in a metabolic half-life of less than one minute. After intracavernosal administration, levels of alprostadil and its primary metabolite 15-oxo-13,14,-dihydro-PGE$_1$ are elevated in the cavernosa. No intact alprostadil is detected in the peripheral circulation, and levels of the 15-oxo-13,14,-dihydro-PGE$_1$ metabolite are not significantly elevated in the peripheral circulation after intracavernosal administration.

5.3 Preclinical Safety Data

Impairment of fertility/Effect on reproduction
Rat reproductive studies indicate that alprostadil at doses of up to 0.2 mg/kg/day (subcutaneous) (200 times the maximum human recommended dose of 60 µg) did not have an adverse effect on the reproductive potential of the male rat.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

CAVERJECT® is not intended to be mixed or co-administered with any other products. The presence of benzyl alcohol in the reconstitution vehicle decreases the degree of binding to package surfaces. Therefore, a more consistent product/delivery is produced when bacteriostatic water for injection containing benzyl alcohol is used.

6.2 Storage

Store below 30°C.

The expiry date (month/year) is mentioned on the package after “EXP.:” (EXP. = expiry date).

7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York 10017
United States

CAV-SIN-0422/0
Date of last revision: April 2022