

PRESCRIBING INFORMATION

Caverject™

Alprostadil



COMPOSITION

- CAVERJECT™ 10 µg
Each powder vial contains: alprostadil 10 µg, lactose, alpha cyclodextrine, sodium citrate.
When necessary pH was adjusted with sodium hydroxide and/or hydrochloric acid.
Each ml of diluent contains: benzyl alcohol, water for injection q.s. 1 ml.
- CAVERJECT™ 20 µg
Each powder vial contains: alprostadil 20 µg, lactose, alpha cyclodextrine, sodium citrate.
When necessary pH was adjusted with sodium hydroxide and/or hydrochloric acid.
Each ml of diluent contains: benzyl alcohol, water for injection q.s. 1 ml.

FORMS, WAYS OF ADMINISTRATION AND PACKAGES

Pharmaceutical form after reconstitution: injectable solution.

Way of administration: intracavernosal.

Packages:

- Vial with 10 µg alprostadil + pre-filled syringe with 1 ml bacteriostatic water for injection + 2 needles (22G1½ and 27G1½).
- Vial with 20 µg alprostadil + pre-filled syringe with 1 ml bacteriostatic water for injection + 2 needles (22G1½ and 27G1½).

PROPERTIES

Pharmacodynamics

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 alpha₁-adrenergic activity in penile tissue and by its relaxing effect on cavernosal smooth muscle.

Pharmacokinetics

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-PGE₁ are elevated in the cavernosa. No intact alprostadil is detected in the peripheral circulation, and levels of the 15-oxo-13,14-dihydro-PGE₁ metabolite are not significantly elevated in the peripheral circulation after intracavernosal administration.

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.

DOSAGE AND ADMINISTRATION

CAVERJECT™ is administered by direct intracavernosal injection. A 1½-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 20 micrograms; however, since 99% of patients received doses of 20 micrograms or less, doses of greater than 20 micrograms are not recommended. In general, the lowest possible effective dose should always be employed.

Initial Titration in Physician's Clinic

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. 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 clinic until complete detumescence occurs.

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

Maintenance Therapy

The first injections of CAVERJECT™ must be done at the physician's clinic 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 clinic. 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 clinic 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. The product should be inspected visually for particulate matter and discoloration prior to administration.

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, ¹³³xenon 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.

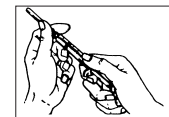
1. Wash your hands with soap and water.
2. Remove the plastic cap from the vial.
3. Wipe the rubber stopper of the vial, using one of the swabs provided (the second swab is needed later). Discard the used swab.

Wiping the rubber stopper of a vial



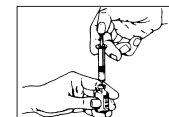
4. Unwrap the larger needle (labelled 22G1½), keeping its plastic needle cover in place. Join it to the syringe by slipping the collar of the needle over the neck of the syringe and pushing firmly.

Joining the needle to the syringe



5. Carefully remove the needle cover.
6. Holding the syringe and the needle pointing upward, push the plunger to the 1 ml mark on the syringe. (This will get rid of any excess water in the syringe).
7. Pierce the needle through the center portion of the rubber stopper of the vial, and then push down the plunger to inject the water into the vial.

Injecting bacteriostatic water into the vial



8. Carefully holding the syringe and vial as a unit, gently swirl until the powdered medication dissolves completely. DO NOT USE if the resulting solution is cloudy or colored, or it contains particles.

Withdrawing the Medication

1. To withdraw the medication, turn the vial upside down with the syringe in place. Making sure to keep the tip of the needle below the level of the fluid, slowly withdraw the plunger of the syringe until the amount of solution is level with the line recommended by your doctor.
2. If there are air bubbles in the syringe, tap the syringe gently to expel the air, or inject the solution back into the vial and slowly withdraw again.

Tapping the syringe to remove air bubbles



3. Remove the needle from the vial and carefully replace the needle cover on the needle.
4. Open the packaging of the smaller needle (labelled 27G1½), without removing the needle, and put it to one side.
5. Remove the large needle and cap from the syringe and discard.
6. Holding the syringe in one hand, take the smaller needle from its open packet, keeping the plastic needle cover in place, and join it to the syringe in the same way that you put on the large needle.

Self-injecting the Medication

Cross-section of the penis showing injection sites

Veins, arteries, nerves

Corpora cavernosa (both)

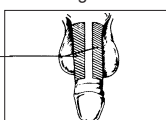
Urethra

Injection sites: Needle correctly entering one of the corpora cavernosa

Diagram A



Diagram B



Top view of penis showing injection sites

Injection sites

The medication is to be injected into either of two areas of the penis called the corpora cavernosa.

1. Perform the self-injection procedure while sitting in an upright or slightly reclining position.
2. Use only the injection areas shown in diagrams A and B.
Alternate the injection sites each time you use CAVERJECT™: choose one side for this injection, use the other side next time, and so on. Within either area, the actual point of injection should 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 during the procedure. In uncircumcised men the foreskin must be retracted to assure proper placement of the injection.
4. Clean the injection area thoroughly with the unused alcohol swab. Put the swab to one side.
5. Hold the syringe between your thumb and index finger. Do not put your thumb on the plunger. With a steady, continuous motion, insert the needle at a 90-degree angle into the injection site as directed by your doctor.
Avoid visible blood vessels.

Inserting the needle into the injection site



6. Move your thumb or forefinger to the top of the plunger and press down. Inject the entire contents of the syringe in a slow, steady motion.

Injecting the contents of the syringe



7. Withdraw the needle from your penis. Squeezing both sides of the penis, apply pressure with the alcohol swab to the injection site for about 3 minutes. If bleeding occurs, maintain pressure until the bleeding stops.
8. 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. If not, the plastic CAVERJECT™ pack may be used as follows: put the used syringe, needles and vial into the plastic CAVERJECT™ container. Then remove the red plastic locking device from the container and place to one side. Close the container firmly so that it snaps shut.
Remove the perforated center portion of the CAVERJECT™ label to uncover a keyway. To lock the container shut, push the red locking device completely into the keyway. Once the locking device is in position, the CAVERJECT™ container will be permanently closed and can now be discarded safely. Because it contains the used syringe, needles and vials, it should not be recycled.

CONTRA-INDICATIONS

CAVERJECT™ should not be used in patients who have a known hypersensitivity to the drug or to other prostaglandins, or 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.

ADVERSE REACTIONS

The following adverse reactions information was obtained from clinical studies sponsored by Upjohn involving 1712 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 during erection at least once, however, this event was associated with only 11% of the administered injections. In the majority of the cases, burning sensation or tension in the penis 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 hours) was 2%. The frequency of priapism (defined as an erection that lasts 4 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 fewer than 1% of patients: balanitis, injection site hemorrhage, injection site inflammation, injection site itching, injection site swelling, urethral bleeding, and penile warmth, numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, 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, hypesthesia, buttock weakness, localized pain (buttocks pain, leg pain, genital pain, abdominal pain), headache, pelvic pain, back pain, flu syndrome, cardiac arrhythmias, shock and collapse.

Hemodynamic changes, manifested as decreases in blood pressure and increases in pulse rate, were observed during clinical studies, principally at doses above 20 micrograms and above 30 micrograms of CAVERJECT™, respectively, and appeared to be dose-dependent. Only three patients (0.2%) discontinued the treatment because of symptomatic hypotension. CAVERJECT had no clinically important effect on serum or urine laboratory tests.

SPECIAL PRECAUTIONS

- a. Priapism (erection lasting over 4 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 4 hours. Treatment of priapism should be according to established medical practice.
- b. Painful erection is more likely to occur in patients with anatomical deformations of the penis, such as angulation, phimosis, cavernosal fibrosis, Peyronie's disease or plaques. 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 increased propensity for bleeding after intracavernosal injection.
- d. Underlying treatable medical causes of erectile dysfunction should be diagnosed prior to initiation of therapy with CAVERJECT™.
- e. Use of CAVERJECT™ offers no protection from the transmission of sexually transmitted diseases. 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 human immunodeficiency virus (HIV).

INCOMPATIBILITIES

CAVERJECT is not intended to be mixed or coadministered 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.

INTERACTIONS

No known interactions. CAVERJECT™ is not intended for coadministration with any other agent for the treatment of erectile dysfunction.

PREGNANCY AND LACTATION

Not applicable.

ABILITY TO DRIVE AND TO OPERATE MACHINERY

Not applicable.

OVERDOSAGE

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 4 hours or longer.

STORAGE

Store at room temperature below 25°C.
For immediate use after reconstitution.

The expiry date (month/year) is mentioned on the package after "EXP" (EXP. + expiry date).

DISPENSING

On medical prescription only.

Manufacturer: Pfizer Manufacturing Belgium NV/SA.

License Holder: Pfizer PFE Pharmaceuticals Israel Ltd.,
9 Shenkar St., Herzliya Pituach 46725.

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