Caverject™

Upjohn

Alprostadil

Composition

- CAVERJECT™ 10μg
  Each powder vial contains:
  Alprostadil 10μg - lactose - sodium citrate. When necessary pH was adjusted with sodium hydroxide and/or hydrochloric acid.
  Each ml of diluent contains:
  Benzyl alcohol - water for injection.
- CAVERJECT™ 20μg
  Each powder vial contains:
  Alprostadil 20μg - lactose - sodium citrate. When necessary pH was adjusted with sodium hydroxide and/or hydrochloric acid.
  Each ml of diluent contains:
  Benzyl alcohol - water for injection.

Forms, ways of administration and packages

Pharmaceutical form after reconstitution: injectable solution.
Way of administration: intracavernosal.
Packages:

- Vial with 10μg alprostadil + ampoule with 1ml bacteriostatic water for injection + empty syringe + 2 needles (22G1½ and 27G½).
- Vial with 10μg alprostadil + pre-filled syringe with 1ml bacteriostatic water for injection + 2 needles (22G1½ and 27G½).
- Vial with 10μg alprostadil + pre-filled syringe with 1ml bacteriostatic water for injection and attached needle.
- Vial with 20μg alprostadil + ampoule with 1ml bacteriostatic water for injection + empty syringe + 2 needles (22G1½ and 27G½).
- Vial with 20μg alprostadil + pre-filled syringe with 1ml bacteriostatic water for injection + 2 needles (22G1½ and 27G½).
- Vial with 20μg alprostadil + pre-filled syringe with 1ml bacteriostatic water for injection and attached needle.

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 alpha$_1$-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-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.

Indications

a. Intracavernosal alprostadil (CAVERJECT™) is indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.
b. Intracavernosal alprostadil (CAVERJECT™) may be a useful adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

Dosage and administration

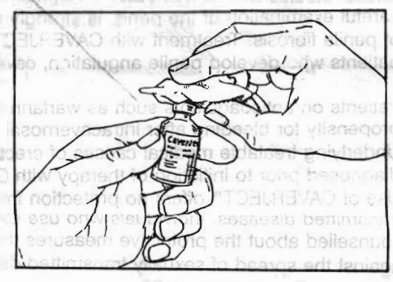
CAVERJECT™ is administered by direct intracavernosal injection. A 1/2-inch, 27- to 30-gauge needle is generally recommended.
The dose of CAVERJECT™ should be individualized for each patient by careful titration under supervision by the physician. In clinical studies, patients were treated with CAVERJECT™ in doses ranging from 0.2 to 140 micrograms; however, since 99% of patients received doses of 60 micrograms or less, doses of greater than 60 micrograms 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. 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	1.25mcg	2.5mcg
Second dose to inject	2.5mcg	Partial response: 5.0mcg No response: 7.5mcg
Third dose to inject	5.0mcg	
Additional increments increases until optimal dose is achieved	5.0mcg	5.0 - 10.0mcg

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 48 hours at room temperature or for 7 days under refrigeration. 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, ^{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.

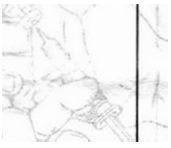
DILUTION AND SELF-INJECTION PROCEDURE USING THE EMPTY SYRINGE WITH DETACHED NEEDLE
This guide is not meant to substitute for the advice and counsel of your doctor.
1. Wash your hands with soap and water.
2. Remove the plastic cap from the vial.
3. Wipe the rubber stopper of the vial, using one of the swabs provided (the second swab is needed later). Discard the used swab.

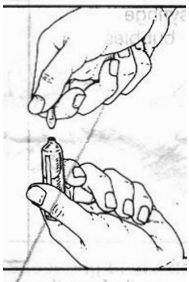
Wiping the rubber stopper of a vial



4. Snap the top off the ampoule (press against coloured dot) and place the ampoule upright on a flat surface.

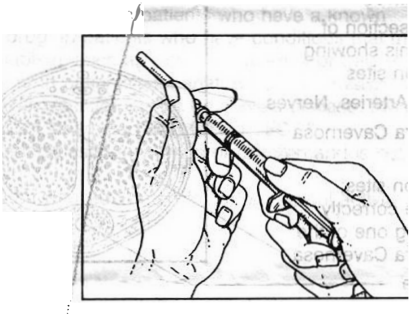
Snapping the top off the ampoule





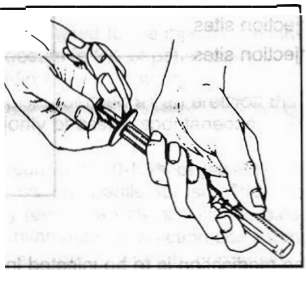
5. Remove the syringe from its wrapping.
6. Unwrap the larger needle (labelled 22G1 ½), keeping its plastic needle cover in place. Join it to the syringe by slipping the collar of the needle over the neck of the syringe and pushing firmly.
7. Carefully remove the needle cover.
8. Insert the needle into the ampoule.

Joining the needle to the syringe



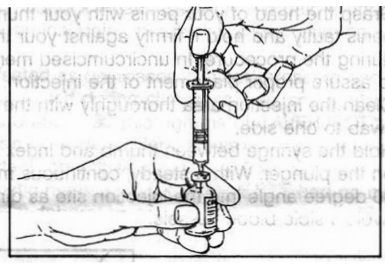
9. With the needle pointing down, hold the ampoule and syringe in one hand, and use the other hand to withdraw the plunger of the syringe, being careful to keep the tip of the needle below the surface of the bacteriostatic water in the ampoule. When the level of water in the syringe exceeds the 1ml line printed on the side, withdraw the syringe from the ampoule.

Withdrawing bacteriostatic water from the ampoule



10. Holding the syringe and the needle pointing upward, push the plunger to the 1ml mark on the syringe. (This will get rid of any excess water in the syringe).
11. Pierce the needle through the centre 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



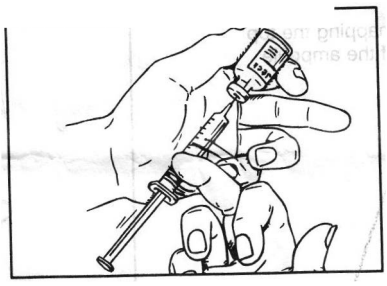
12. Carefully holding the syringe and vial as a unit, gently swirl until the powdered medication dissolves completely. DO NOT USE if the resulting solution is cloudy or coloured, or it contains particles.
13. Withdraw the syringe from the vial, replace the needle cap, and put the syringe to one side.
14. Open the packaging of the smaller needle (labelled 27G½), without removing the needle, and put it to one side.
15. Remove the large needle and cap from the syringe and discard.
16. Holding the syringe in one hand, take the smaller needle form 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.
17. Carefully remove this needle cover and insert the smaller needle into the hole you have already made in the rubber stopper of the vial.

WITHDRAWING THE MEDICATION

18. 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.

9. 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



20. Remove the needle from the vial and carefully replace the needle cover on the needle.

SELF-INJECTING THE MEDICATION

Diagram A

Cross-section of the penis showing injection sites

Veins, Arteries, Nerves

Corpora Cavernosa (both)

Injection sites; Needle correctly entering one of the Corpora Cavernosa

Urethra

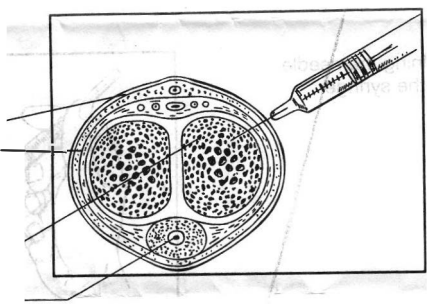
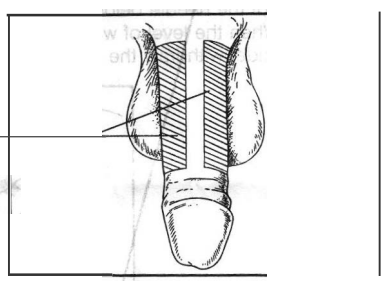


Diagram B

Top vieuw of penis showing injection sites

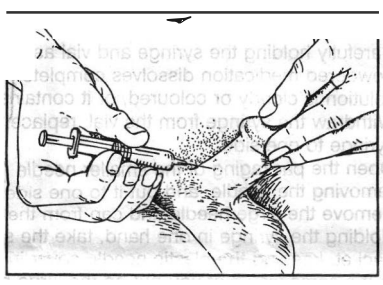
Injection sites



The medication is to be injected into either of two areas of the penis called the corpora cavernosa (see diagrams A and B above).

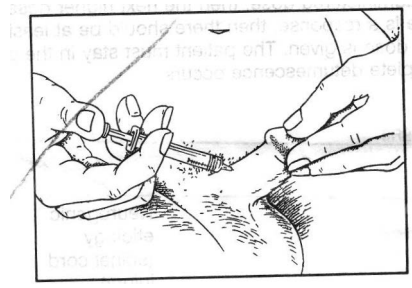
21. Perform the self-injection procedure while sitting in an upright or slightly reclining position.
22. Use only the injection areas shown in diagrams A and B.
Alternate the injection sites each time you use CAVERJECT™: choose one side for this injection, use the other side next time, and so on. Within either area, the actual point of injection should be changed each time.
23. 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.
24. Clean the injection area thoroughly with the unused alcohol swab. Put the swab to one side.
25. Hold the syringe between 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



26. 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 .



27. 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.
28. 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. Do not re-use or share needles or syringes.

Contra-indications

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.

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 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 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.
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. 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.

Special precautions

a. 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.
b. 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.
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 6 hours or longer.

Storage
Store in refrigerator (2°-8°C).
The expiry date (month/year) is mentioned on the package after "EXP.:" (EXP. = expiry date).

Dispensing
On medical prescription only.

Manufacturer: Upjohn s.a. - Puurs - Belgium

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