CAVERJECT

Alprostadil

20µg Powder and solvent for solution for injection

Reference market: Belgium

AfME Markets using same as LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

Warning

Apnea is experienced by about 10 to 12% of neonates with congenital heart defects treated with alprostadil. Apnea is most often seen in neonates weighing less than 2 kg at birth and usually appears during the first hour of drug infusion. Therefore, respiratory status should he monitored throughout treatment, and alprostadil should be used where ventilatory assistance is immediately available

1. NAME OF THE MEDICINAL PRODUCT

CAVERJECT 20 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CAVERJECT 20 micrograms: each vial contains 20 micrograms Alprostadil.

Excipient with known effect:
The solvent contains benzyl alcohol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic or mixed etiology.
Useful adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

CAVERJECT is not indicated for paediatric use (see section 4.4).

4.2 Posology and method of administration

Posology

Based on the possible complications of intracavernous injection of vaso-active drugs, it is recommended that the diagnosis and the initial dose should be determined by a physician-specialist.

CAVERJECT TO THE DIAGNOSIS OF ERECTILE DYSFUNCTION
After an intracavernous injection of CAVERJECT, the occurrence of an erection is monitored.
To allow assessment of penile vasculature, CAVERJECT can be used as an adjunct to laboratory investigations such as duplex or Doppler imaging, Xenon washout tests, radioisotope penogram and penile arteriography.
For any of these tests, a single dose of CAVERJECT that induces an erection with firm rigidity should be used.

INITIAL TITRATION IN PHYSICIAN'S OFFICE
The first injection of CAVERJECT must be done at the physician's office by medically trained personnel.

The patient must stay in the physician's office until complete detumescence occurs. During titration no more than two doses should be given within a 24-hour period. If there is a partial response, then there should be at least a 1-day interval before the next dose is given. If there is no response, it is also advisable to wait at least 1 day.

Erectile dysfunction of vasculogenic, psychogenic or mixed etiology.
Dosage titration should be initiated at 2.5 micrograms of alprostadil. If there is only a partial response, the dose may be increased to a dose of 5 micrograms and then in increments of 5 to 10 micrograms, until an erection suitable for intercourse is produced. It is recommended that the administered dose produces a duration of the erection not exceeding one hour. The patient must stay in the physician's office until complete detumescence occurs.
If there is no response to the initial 2.5 micrograms dose, the second dose may be increased to 7.5 micrograms, followed by increments of 5 to 10 micrograms. If there is a partial response, then there should be at least a 1-day interval before the next dose is given. If there is no response, it is also advisable to wait at least 1 day.

Erectile dysfunction of neurogenic etiology (Spinal Cord Injury)
Dosage titration should be initiated at 1.25 micrograms of alprostadil. The dose may be increased by 1.25 micrograms to a dose of 2.5 micrograms, followed by an increment of 2.5 micrograms to a dose of 5 micrograms, and then in 5 micrograms increment until an erection suitable for intercourse is produced. It is recommended that the administered dose produces a duration of the erection not exceeding one hour. The patient must stay in the physician's office until complete detumescence occurs. If there is a partial response, then there should be at least a 1-day interval before the next dose is given. If there is no response, it is also advisable to wait at least 1 day.

The following table gives an overview of the dosage schedule in relation to the etiology :

	Neurogenic etiology (Spinal Cord Injury)	**Vasculogenic, psychogenic or mixed etiology**
Starting dose	1;25 micrograms	2.5 micrograms
Second dose	2.5 micrograms	Partial response: 5 micrograms No response: 7.5 micrograms
Third dose	5.0 micrograms	
Further dose titration	5.0 micrograms	5 to 10 micrograms

In clinical studies, patients were treated with CAVERJECT in doses ranging from 0.2 to 140 micrograms. More than 80% of the treated patients experienced an erection sufficient for sexual intercourse.

Paediatric population
CAVERJECT must not be used in the paediatric population (see section 4.3 Contraindications and 4.4 Special warning and precautions to use, benzyl alcohol).

Method of administration

MAINTENANCE THERAPY
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 intracavernous injection must be done under sterile conditions. The dose of CAVERJECT that is selected for self-injection treatment should provide the patient with an erection that is satisfactory for sexual intercourse it is recommended that the administered dose produces a

duration of the erection not exceeding one hour. If the duration of erection is longer than 1 hour, the CAVERJECT dose should be reduced. Self-injection therapy for use at home should be initiated at the dose that was determined by the physician. In general, the lowest possible effective dose should be employed. However, the physician should consider the wishes of the individual patient when defining the dose for self-injection. If required, and only after consultation with the physician, the dose may be adjusted in accordance with the titration guidelines described above. Careful and continuous follow-up of the patient while in the self-injection program must be exercised, especially during the initial self-injections, since adjustments in the CAVERJECT dose may be needed. Since 99% of patients received doses of maximum 60 micrograms, doses of greater than 60 micrograms are not recommended.
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 safe disposal of the injection syringe, injection needles and vial. While on self-injection treatment, the patient should visit the prescribing physician's office every 3-4 months. At that time, the efficacy and safety of the therapy should be assessed, and the dose of CAVERJECT should be adjusted, if needed. This was the case for up to 57% of patients in one clinical study. The effectiveness of CAVERJECT for long-term use has been documented in an uncontrolled, self-injection study. The mean dose of CAVERJECT at the end of 6 months was about 20 micrograms.

PREPARATION OF THE SOLUTION
The lyophilized powder is packaged in a 5ml vial.
The enclosed bacteriostatic water for injection (benzyl alcohol) of 1 ml must be added to the vial. After reconstitution by addition of 1 ml of bacteriostatic water for injection, the resulting solution will contain 20 micrograms per milliliter of alprostadil, 172 milligrams per ml of lactose, and 47 micrograms per ml of sodium citrate. Once reconstituted, no additional materials should be injected into the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

INJECTION OF THE SOLUTION IN THE PENIS
CAVERJECT is administered by direct intracavernous injection. A 27 to 30 Gauge 1/2 inch injection needle is recommended.
The site of injection is usually along the dorso-lateral aspect of the proximal third of the penis. The injection site must be cleansed with an alcohol swab. It is recommended to regularly alter the side of the penis that is injected. Injecting in visible veins should be avoided.

4.3 Contraindications

Intracavernous alprostadil should not be used:
- in patients who have an hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- in patients prone to priapism due to sickle cell anaemia or latent sickle cell disease (without anaemia), multiple myeloma or leukaemia
- in patients with anatomical deformation of the penis, such as angulation, phimosis, cavernosal fibrosis, or Peyronie's disease.
- in patients with penile implants
- in men for whom sexual activity is inadvisable or contraindicated
- in premature babies or neonates (see section 4.4) and children.

4.4 Special warnings and precautions for use

Underlying treatable medical causes of erectile dysfunction should be diagnosed and treated prior to initiation of therapy with alprostadil.

Priapism

Prolonged erection and/or priapism (erection lasting over six hours) are known to occur following intracavernous administration of vasoactive substances, including alprostadil. In order to minimise this risk, the lowest effective dose should be selected; patients should be instructed to immediately report to a physician any erection lasting for an overly prolonged time period, such as 4 hours or longer. Treatment of priapism should not be delayed more than 6 hours (see section 4.9). The treatment of priapism should be according to established medical practice. The treatment of priapism may include different approaches such as aspiration, intracavernous injection of sympathomimetic amines or surgery. In evaluating a patient for alprostadil therapy, the physician should determine which of these interventions would be appropriate for the individual patient.

Penile fibrosis

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.

Penile fibrosis, including angulation, cavernosal fibrosis, fibrotic nodules and Peyronie's disease may occur following the intracavernous administration of alprostadil. Fibrosis may occur more frequently with prolonged use.

Regular controls and careful examination of the penis are highly recommended to detect early signs of fibrosis or Peyronie's disease.

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 HIV

Use of intracavernous alprostadil offers no protection from the transmission of sexually transmitted diseases. Individuals who use alprostadil 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). Injection of CAVERJECT can induce a small amount of bleeding at the site of injection (see Undesirable effects), which could increase transmission of such diseases.

Anticoagulants

Patients on anticoagulants, such as warfarin or heparin, may have an increased risk of bleeding after intracavernous injection.

CAVERJECT should be used with caution in patients with cardiovascular and cerebrovascular risk factors.

Alprostadil should be used with caution in patients who have experienced transient ischaemic attacks or those with unstable cardiovascular disorders.

Sexual stimulation and intercourse can lead to cardiac and pulmonary events in patients with coronary heart disease, congestive heart failure or pulmonary disease. These patients when using alprostadil should engage in sexual activity with caution.

Alprostadil is not intended for co-administration with any other agent for the treatment of erectile dysfunction (see also 4.5).

The potential for abuse of alprostadil should be considered in patients with a history of psychiatric disorder or addiction.

Reconstituted solutions of alprostadil are intended for single use only. The injection delivery system/syringe and any remaining solution should be properly discarded.

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.

Excipient information

Benzyl alcohol
The solvent contains benzyl alcohol. Benzyl alcohol may cause allergic reactions.

The combined daily metabolic load of benzyl alcohol from all sources should be considered, as high volumes should be used with caution and only if necessary, especially in patients with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

This medicine is only indicated for intracavernosal injection. Intravenous administration of the preservative benzyl alcohol has been associated with serious adverse events and death in paediatric patients including neonates ("gasping syndrome"). The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants may be more likely to develop toxicity. CAVERJECT powder and solvent for solution for injection is not indicated for paediatric use.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Potential pharmacokinetic drug interactions between CAVERJECT and other substances have not been formally studied. In clinical studies concurrent use of diuretics, antidiabetic agents (including insulin) or non-steroid anti-inflammatory agents did not have any effect on the safety or efficacy of CAVERJECT.

The effects of combinations of alprostadil with other treatments for erectile dysfunction (e.g. sildenafil) or other drugs inducing erection (e.g. papaverine) have not been formally studied. Such agents should not be used in combination with alprostadil due to the potential for inducing prolonged erections.

Sympathomimetics may reduce the effect of alprostadil. Alprostadil may enhance the effects of antihypertensives, vasodilative agents, anticoagulants and platelet aggregation inhibitors.
Patients on anticoagulants such as warfarin or heparin may have increased propensity for bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation
Not applicable

Fertility
In a study in male rats, alprostadil had no effect on reproductive function (see section 5.3).

4.7 Effects on ability to drive and use machines

Alprostadil would not be expected to have an influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequent adverse effects following an intracavernous injection was pain in the penis. 30% of patients reported pain at least once. Pain was associated with 11% of the injections administered. In most cases pain was assessed as mild or moderate. 3% of patients discontinued treatment because of pain.

Penile fibrosis, including angulation, fibrotic nodules and Peyronie's disease, was reported in 3% of clinical trial patients overall. In one self-injection study in which the duration of use was up to 18 months, the incidence of penile fibrosis was higher, approximately 8%.

Haematoma and ecchymosis at the injection site, which is related with the injection technique rather than the effect of alprostadil, was reported by 3% and 2% of patients, respectively.

Prolonged erection (an erection for 4-6 hours) developed in 4% of patients. Priapism (a painful erection for more than 6 hours) occurred in 0.4%. In most cases it disappeared spontaneously.

Adverse drug reactions reported during clinical trials and post marketing experience are presented in the table below, frequencies are very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); not known (cannot be estimated from the available data). The adverse drug reactions are listed in order of decreasing medical seriousness within each frequency category and system organ class.

System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Not known (cannot be estimated from the available data)**
Infections and infestations			Fungal infection, Common cold	
Nervous system disorders			Presyncope, Hypoaesthesia, Hyperaesthesia, Headache	Cerebrovascular accident
Eye disorders			Mydriasis	
Cardiac disorders			Supraventricular extrasystoles	Myocardial ischaemia
Vascular disorders		Haematoma	Venous haemorrhage, Hypotension*, Vasodilatation, Peripheral vascular disorder, Vein disorder	
Gastrointestinal disorders			Nausea, Dry mouth	

Skin and subcutaneous tissue disorders		Erythema	Rash, Hyperhidrosis, Pruritus	
Musculoskeletal and connective tissue disorders		Muscle spasms	Pain in the hip and back, Weakness in the muscles of the thigh, Pain in the thighs, legs, and in the abdomen	
Renal and urinary disorders			Urethral haemorrhage, Haematuria, Dysuria, Pollakiuria, Micturition urgency	
Reproductive system and breast disorders	Penile Pain	Peyronie's disease, Penis disorder, Erection increased	Priapism, Pelvic pain, Testicular mass, Spermatocele, Testicular swelling, Testicular oedema, Testicular disorder, Scrotal pain, Scrotal erythema, Scrotal oedema, Testicular pain, Scrotal disorder, Painful erection, Balanitis, Phimosis, Erectile dysfunction, Ejaculation disorder	
General disorders and administration site conditions		Injection site haematoma, Haematoma, Ecchymosis	Haemorrhage, Injection site haemorrhage, Inflammation, Injection site inflammation, Injection site warmth, Injection site oedema, Injection site swelling, Injection site pain, Injection site irritation, Asthenia, Injection site anaesthesia, Oedema, Oedema peripheral, Injection site pruritus, Pain or tightness, Flu-syndrome	
Investigations			Blood creatinine increased, Blood pressure decreased, Heart rate increased*	

* Dose-dependent haemodynamic changes were observed such as drop in blood pressure and rapid heart beat, with doses exceeding 20 or 30 micrograms respectively. These changes were usually not clinically significant: only 3 out of the 1712 patients in the clinical studies discontinued treatment because of symptomatic hypotension.

In some patients the systemic effects are more likely to be due to the injection procedure than to the pharmacological properties of alprostadil. The results of serum and urine analyses were not affected by the use of CAVERJECT.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

To report side effects:

- **Saudi Arabia**

The National Pharmacovigilance Centre (NPC)
- SFDA call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

- **Other GCC States**

- *Please contact the relevant competent authority.*

4.9 Overdose

Overdosage was not observed in clinical trials with alprostadil. If intracavernous overdose of CAVERJECT occurs, the patient should be placed 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.
In man, prolonged erection and/or priapism are known to occur following intracavernous administration of vasoactive substances, including alprostadil. The treatment of priapism should be according to established medical practice. The treatment of priapism may include different approaches such as aspiration, intracavernous injection of sympathomimetic amines or surgery. When evaluating the patient before alprostadil therapy, the physician will determine what kind of intervention is most suitable for the individual patient. Patients should be instructed to report to a physician any erection lasting for a prolonged time period, such as 4 hours or longer.

The treatment of priapism (prolonged erection) should not be delayed more than 6 hours. Initial therapy should be by penile aspiration. Using aseptic technique, insert a 19-21 gauge butterfly needle into the corpus cavernosum and aspirate 20-50 ml of blood. This may detumesce the penis. If necessary, the procedure may be repeated on the opposite side of the penis until a total of up to 100 ml blood has been aspirated. If still unsuccessful, intracavernous injection of alpha-adrenergic medication is recommended. Although the usual contra-indication to intrapenile administration of a vasoconstrictor does not apply in the treatment of priapism, caution is advised when this option is exercised. Blood pressure and pulse should be continuously monitored during the procedure. Extreme caution is required in patients with coronary heart disease, uncontrolled hypertension, cerebral ischaemia, and in subjects taking monoamine oxidase inhibitors. In the latter case, facilities should be available to manage a hypertensive crisis. A 200 microgram/ml solution of phenylephrine should be prepared, and 0.5 to 1.0 ml of the solution injected every 5 to 10 minutes. Alternatively, a 20 microgram/ml solution of epinephrine should be used. If necessary, this may be followed by further aspiration of blood through the same butterfly needle. The maximum dose of phenylephrine should be 1 mg, or epinephrine 100 micrograms (5 ml of the solution). As an alternative metaraminol may be used, but it should be noted that fatal hypertensive crises have been reported. If this

still fails to resolve the priapism, urgent surgical referral for further management, which may include a shunt procedure is required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction
ATC code: G04BE01

Alprostadil or prostaglandin E_1 is one of a family of naturally-occurring acidic lipids. Vasodilation and inhibition of platelet aggregation are among the most notable pharmacological effects. Alprostadil, when given by intracavernous injection, induces erection in men. The erection usually starts within 10-30 minutes after injection. The duration of erection is dose-dependent. Alprostadil induces erection by relaxation of trabecular smooth muscle and by dilation of cavernosal arteries. This leads to expansion of lacunar spaces and entrapment of blood by compressing venules against the tunica albuginea.

5.2 Pharmacokinetic 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 intracavernous administration, levels of alprostadil and its primary metabolite 15-oxo-13,14-dihydro-PGE1 are elevated in the corpora cavernosa. No intact alprostadil is detected in the peripheral circulation, and levels of the 15-oxo-13,14-dihydro-PGE1 metabolite are here not significantly elevated.

5.3 Preclinical safety data

Long term carcinogenicity studies have not been conducted. A standard battery of genotoxicity studies revealed no mutagenic potential of alprostadil.

Alprostadil at subcutaneous doses of up to 0.2 mg/kg/day (200 times the maximum recommended human intracavernous dose) had no adverse effects on reproductive function in male rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CAVERJECT lyophilized powder: lactose monohydrate, sodium citrate, dilute hydrochloric acid, sodium hydroxide.

Solvent: benzyl alcohol, water for injection.

6.2 Incompatibilities

No known incompatibilities. CAVERJECT is not intended for simultaneous injection with any other agent for the treatment of erectile dysfunction.

6.3 Shelf life

Do not use Caverject after the expiry date which is stated on the carton after EXP:.
Shelf life: 3 years.

The expiry date (month/year) is mentioned on the package after "EXP:" (EXP = expiry date).
When stored in the original container, the reconstituted alprostadil solution is physically and chemically stable for a period of 24 hours at (2°C - 8°C). Reconstituted solutions should not be frozen.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

CAVERJECT 20 micrograms powder and solvent for solution for injection:
1 vial with powder + 1 ampoule with 1 ml solvent

6.6 Special precautions for disposal

Keep out of the sight and reach of children.
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MARKETING AUTHORISATION HOLDER
Pfizer SA, Belgium.

MANUFACUTRED BY
Pfizer Manufacturing Belgium NV, Belgium

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04-April-2001

9. DATE OF REVISION OF THE TEXT

October 2023