PRODUCT INFORMATION

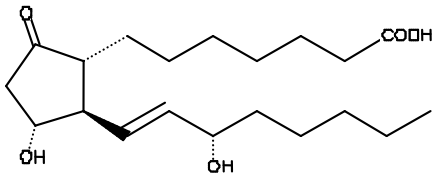
Caverject®
(alprostadil)

NAME OF THE MEDICINE

The Australian Approved Name is Alprostadil, Prostaglandin $E_{1,}$ (PGE_1).

The chemical name is (*11α*,13*E*,15*S*)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid and the CAS number is 745-65-3.

The molecular weight is 354.49 and the structural formula is:



DESCRIPTION

Alprostadil is the naturally occurring form of PGE_1.

Alprostadil is a white to off-white crystalline powder with a melting point between 115°C - 116°C. Alprostadil has a solubility of 8,000 micrograms in 100 mL double distilled water at 35°C.

Caverject is available as a sterile freeze-dried powder for intracavernosal injection only. It is supplied in clear glass vials delivering either 10 or 20 micrograms of alprostadil. In addition to alprostadil, the freeze-dried powder in Caverject also contains lactose monohydrate, alpha-cyclodextrin, sodium citrate dihydrate, hydrochloric acid and sodium hydroxide. The diluent (bacteriostatic Water for Injections) provided contains Water for Injections preserved with 9.45 mg/mL benzyl alcohol.

PHARMACOLOGY

Pharmacodynamics

Alprostadil (PGE_1) is one of a family of naturally occurring acidic lipids. Vasodilation and inhibition of platelet aggregation are among the most notable pharmacological effects. In regard to the penile structures, in most animal species tested, alprostadil had relaxant actions 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 contracted by either noradrenaline or PGE_{2a}. 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.

Alprostadil, when given by intracavernosal injection, induces erection in men with erectile dysfunction. The erection usually starts within 5 - 20 minutes after injection and 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, a process referred to as the corporal veno-occlusive mechanism.

Pharmacokinetics

Metabolism

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 metabolised 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

Intracavernosal alprostadil (PGE_1) is indicated for the treatment of erectile dysfunction in adult males. Intracavernosal alprostadil may be a useful adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

CONTRAINDICATIONS

Intracavernosal alprostadil should not be used in patients who have a known hypersensitivity to alprostadil, the active ingredient in Caverject or any of the excipients, or in patients who have conditions that might predispose them to priapism such as sickle cell anaemia, multiple myeloma or leukaemia. Patients with pre-existing penile fibrosis should not be accepted into intracavernosal self-injection therapy. Caverject should not be used in patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis or Peyronie's disease.

Caverject should not be used in men for whom sexual activity is inadvisable or contraindicated. Caverject should not be used in women. It should not be used in children and is not for use in newborns (see PRECAUTIONS).

Caverject should not be used in patients with penile implants.

PRECAUTIONS

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

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. In evaluating a patient for alprostadil therapy, the physician should determine which of these interventions would be appropriate for the individual patient. Patients should be instructed to report to a physician any erection lasting for an overly prolonged time period, such as 4 hours or longer.

Painful erection is more likely to occur in patients with anatomical deformations of the penis. Penile fibrosis, such as angulation, phimosis, cavernosal fibrosis, fibrotic nodules and Peyronie's disease or plaques, may occur following the intracavernosal administration of Caverject. The occurrence of fibrosis may increase with increased duration of use of Caverject.

Patients should be carefully assessed for pre-existing penile fibrosis before initiation of treatment with intracavernosal Caverject. If pre-existing penile fibrosis is found, the patient should not be accepted into intracavernosal self-injection therapy. This assessment should be made during pharmacologically-induced erection. At regular visits the physician **must** examine the penis carefully, preferably in the erect state, for potential development of fibrotic changes. If there are signs of fibrotic complications, treatment with Caverject must be stopped immediately. During self-injection therapy, the patient must be instructed to report to the physician any unusual new adverse effects such as increased or new penile pain, penile bending, and/or nodule formation in the penile shaft.

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

Caverject can induce a small amount of bleeding at the site of injection (see ADVERSE EFFECTS). In patients infected with blood-borne diseases, this could increase the transmission of such diseases to the partner.

Note: Use of intracavernosal alprostadil offers no protection from the transmission of sexually transmitted diseases. Patients prescribed 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) and blood-borne diseases.

The bacteriostatic Water for Injections provided with Caverject contains benzyl alcohol, which is associated with severe adverse effects, including fatal "gasping syndrome" in paediatric patients. The minimum amount of benzyl alcohol at which toxicity may occur is unknown. The risk of benzyl alcohol toxicity depends on the quantity administered and the capacity of the liver and kidneys to detoxify the chemical. Premature and low birth weight infants may be more likely to develop toxicity.

The possibility of needle breakage exists with Caverject, and careful patient instruction in proper handling and injection techniques is required (see DOSAGE AND ADMINISTRATION).

Effects on Fertility

Subcutaneous doses of PGE_1 of up to 0.2 mg/kg/day does not adversely affect or alter rat spermatogenesis.

Use in Pregnancy

Caverject should not be used in women (see CONTRAINDICATIONS**)**. Alprostadil is an abortifacient and stimulates uterine smooth muscle. Since PGE_1 occurs naturally in seminal fluid at doses greater than would be achieved if the Caverject were inadvertently injected into the urethra, the injected alprostadil would not significantly increase the activity of the endogenous PGE_1. However, patients should be advised that pregnant partners should discuss the use of Caverject with their obstetrician.

Use in Lactation

Caverject should not be used in women (see CONTRAINDICATIONS).

Paediatric Use

Caverject should not be used in paediatric patients (see CONTRAINDICATIONS).

Genotoxicity

No potential for mutagenic activity or genetic toxicity was revealed in assays of gene mutation in bacterial and mammalian cells or in DNA damage assays.

Carcinogenicity

Long term carcinogenicity studies have not been done but no carcinogenic potential is indicated from the mutagenicity studies when PGE_1 is used for erectile dysfunction.

INTERACTIONS WITH OTHER MEDICINES

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

In clinical trials, concomitant use of agents such as antihypertensive drugs, diuretics, antidiabetic agents (including insulin), or non-steroidal anti-inflammatory drugs had no effect on the safety or efficacy of Caverject. The safety and efficacy of combinations of Caverject and other vasoactive agents have not been systematically studied.

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

ADVERSE EFFECTS

Based on a review of studies using alprostadil in the treatment of erectile dysfunction the most frequently reported adverse reaction after intracavernosal injection of alprostadil was penile pain during erection, which was also described as a burning sensation or a tension in the penis. However, the occurrence of pain rarely interfered with sexual intercourse. Haematoma and ecchymosis at the site of injection, which was related to the injection technique rather than to the effects of alprostadil, occurred less frequently. In four clinical studies, the frequency of penile fibrosis (including Peyronie's disease, angulation, and fibrotic nodules) was 4.8%. Complete resolution of the fibrotic pathology was observed in 28% of the patients. Prolonged erection (defined as an erection that lasts for 4 to 6 hours) after intracavernosal administration of Caverject was reported in 4% of patients. The frequency of priapism (defined as an erection that lasts 6 hours or longer) was 0.4%. In the majority of cases, spontaneous detumescence occurred.

Adverse reactions reported by less than 1% of patients in clinical studies are listed below:

System Organ Class	**Adverse Drug Reactions**
Infections and infestations	Yeast infection
Reproductive system and breast disorders	Scrotal oedema Scrotal disorder (redness, pain, spermatocele) Testicular disorder (warmth, swelling, mass, thickening) Testicular pain Haemosiderin deposits in the penis Painful erection

System Organ Class	Adverse Drug Reactions
	Ejaculation abnormal Penile deviations Irritation Penile warmth Balanitis Priapism Pelvic pain Perineal pain Genital pain Phimosis
Renal and urinary disorders	Haematuria Urinary frequency Urinary urgency Urination impaired Urethral bleeding
Cardiac disorders	Supraventricular extrasystoles Arrhythmia
Vascular disorders	Hypotension Peripheral vascular disorder Vasodilatation Venous leak Vagal shock
Nervous system disorders	Vasovagal reaction Hyperaesthesia (systemic) Numbness Sensitivity Collapse Dizziness Headache
Eye disorders	Mydriasis
Skin and subcutaneous tissue disorders	Rash Pruritus Diaphoresis Erythema
Musculoskeletal, connective tissue and bone disorders	Leg cramps Localised pain (buttocks, leg or back)
General disorders and administration site conditions	Injection site haemorrhage Injection site inflammation Injection site oedema Injection site pruritus Injection site swelling Non-generalised weakness
Gastrointestinal disorders	Nausea Dry mouth
Investigations	Blood creatinine increased Changes in blood pressure

In some patients, these adverse events may be related to the injection procedure rather than to the pharmacological effects of alprostadil.

DOSAGE AND ADMINISTRATION

Before initiation of treatment with Caverject, patients should be carefully assessed by a specialist practitioner in erectile dysfunction with appropriate training in the use of this drug. The dose should be titrated carefully according to individual need.

If the erectile dysfunction is known to be of neurogenic or psychogenic aetiology, the generally recommended initial dose of Caverject is 2.5 micrograms with subsequent upward titration of the dose in increments of 2.5 micrograms. If the erectile dysfunction is known to be of arteriogenic origin or due to other organic causes, the generally recommended initial dose of Caverject is 5 micrograms with subsequent upward titration of the dose in increments of 5 micrograms. If the aetiology of the erectile dysfunction is unknown, or the Caverject is being used as an adjunct in the diagnosis of impotence, the generally recommended initial dose of Caverject is 2.5 micrograms, with subsequent upward titration of the dose in increments of 2.5 micrograms.

The dose 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 dose administered produce an erection not exceeding one hour duration. Doses of greater than 60 micrograms of alprostadil are not recommended.

The majority of patients obtain a satisfactory response with doses in the range of 10-20 micrograms. The usual maximum recommended frequency of injection is no more than once in a 24 hour period and no more than three times weekly. No more than three vials must be used for any one treatment.

Caverject is administered by direct intracavernosal injection. A 13 mm, 27 to 30 gauge, needle is recommended. The first injection of Caverject must be done by medically trained personnel. If self-administration is planned, the specialist should make an assessment of the patient's (or as appropriate, the partner's) skill and competence with the procedure. After proper training and instruction, Caverject may be injected at home. While on self-injection treatment, it is recommended that the patient visit the above specialist's office at periodic intervals. At that time, the efficacy and safety of the therapy should be assessed and the dose of Caverject should be adjusted if needed.

Note:

(a) 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 hospitalisation and surgical removal. Careful patient instruction in proper handling and injection techniques may minimise the potential for needle breakage. The patient should be instructed that, if the needle is bent, it must not be used; and no attempt should be made to straighten a bent needle. A bent needle should be removed from the syringe and discarded; and a new, unused, sterile needle attached to the syringe.

(b) Consumer Medicine Information is available from your pharmacist. This information includes a summary of the procedure for self-injection with Caverject; this patient information is only intended to support the instruction provided by medically qualified personnel after a patient has been assessed as competent to manage the procedure.

General Procedure for Reconstitution & Injection

Caverject must be reconstituted, before use, with the supplied diluent (bacteriostatic Water for Injections preserved with benzyl alcohol) as follows:

1. Add 1 mL of diluent to the vial using the 22 gauge needle supplied.

2. Gently shake the vial to mix all contents until dissolved.

   After reconstitution with 1 mL of diluent, the volume of the resulting solution is slightly more than 1 mL but each 1 mL will deliver 10 or 20 micrograms of alprostadil, depending on the product strength.

3. As with all parenteral products, Caverject should be inspected visually for particulate matter and discolouration prior to administration.

4. Using the same needle, withdraw the required dosage and discard any residue left in the vial.

5. Use the 27 to 30 gauge needle provided for injecting.

6. Stretch the penis out across the thigh, with the foreskin retracted in uncircumcised men. Clean the site with an alcohol swab. Inject into either of the two corpora cavernosa (see figure 1); inject at 90 degrees to the skin; the needle should be inserted up to the needle hub to ensure that the corpus is injected.

Figure 1: Intracavernosal injection - showing areas for injection

Note: Subsequent injections should be alternated between the two cavernosa. The injection site should be varied from the base of the penis to just proximal to the glans avoiding the midline and any veins. Injections should not be made into the underside of the penis.

7. After injecting, remove the needle and apply pressure to the injection site with the alcohol swab for about 5 minutes or until any bleeding stops. This procedure should result in an erection that is adequate for intercourse for approximately 30-60 minutes. If the erection is sustained beyond 60 minutes the dose of Caverject should be halved for the next injection.

8. The reconstituted vial of Caverject is intended for single use only and should be discarded after use. The patient should be instructed regarding appropriate injection technique including the need for the use of a new syringe and needle for **each** injection. Following administration the vial and syringe should be discarded; the patient should be instructed in the appropriate disposal of the syringe and needle.

Incompatibilities

Only the accompanying diluent or bacteriostatic Water for Injections with benzyl alcohol should be used when reconstituting Caverject.

OVERDOSAGE

Symptoms

Overdose data is limited. The pharmacotoxic signs of alprostadil are similar in all animal species and include depression, soft stool or diarrhoea and rapid breathing. In man, prolonged erection and/or priapism are known to occur following intracavernosal administration of vasoactive substances, including alprostadil. Patients should be instructed to report to a physician any erection lasting for a prolonged time period, such as 4 hours or longer.

Treatment

Prolonged erection or priapism (lasting more than 6 hours) should be treated to prevent tissue hypoxia and possible necrosis. The treatment of priapism may include different approaches such as aspiration, intracavernosal injection of sympathomimetic amines or surgery.

There is no antidote for alprostadil overdose. Treatment is symptomatic and supportive. Support respiratory and cardiac function. Monitor pulmonary function, vital signs, ECG, pulse oximetry, and fluid and electrolyte status in patients with significant diarrhoea.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Caverject containing 10 or 20 micrograms of alprostadil is supplied in packs of 1, 5 or 10 containing a 5 mL glass vial, a 1 mL pre-filled diluent (bacteriostatic Water for Injections preserved with benzyl alcohol) syringe, two needles (a 22 gauge needle for reconstitution and a 27 to 30 gauge needle for injection) and two swabs.

Not all pack sizes are available.

Storage conditions

Store below 25°C. Protect from moisture.

Use as soon as possible after reconstitution. If storage is necessary, hold at 2-8°C (Refrigerate. Do not freeze) for not more than 24 hours.

Only the accompanying diluent (bacteriostatic Water for Injections preserved with benzyl alcohol) should be used for reconstituting Caverject.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE OF THE MEDICINE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

4 February 2013.

DATE OF MOST RECENT AMENDMENT

19 May 2016.

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