PRODUCT INFORMATION

CAVERJECT® Impulse 10 and 20 microgram

NAME OF DRUG

Non-proprietary name: Alprostadil, Prostaglandin E_1, (PGE_1)

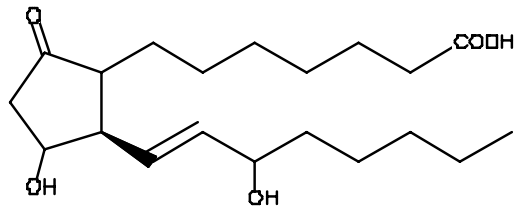
Chemical name: (*11α*, 13*E*, 15*S*)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid

CAS Number: 745-65-3

DESCRIPTION

CAVERJECT (alprostadil) is the naturally occurring form of prostaglandin E_1 (PGE_1).

Alprostadil is a white to off-white crystalline powder with a melting point between 115°C - 116°C and has a molecular weight of 354.49. Alprostadil is practically insoluble in water with a solubility of 8,000 micrograms in 100 mL double distilled water at 35°C. The structural formula is as follows:



CAVERJECT is available as a dual chamber syringe for intracavernosal injection only. The dual chamber glass cartridge contains lyophilised powder and diluent for reconstitution. The front compartment contains 12.8 micrograms or 25.6 micrograms of alprostadil, which corresponds to a maximum dose delivery of 10 or 20 micrograms respectively. In addition to alprostadil, the freeze-dried powder in CAVERJECT Impulse also contains: lactose, alpha-cyclodextrin, sodium citrate, hydrochloric acid solution and sodium hydroxide solution (used for pH adjustment). The rear compartment contains 0.6 mL of Bacteriostatic Water for Injection (benzyl alcohol in water for injections) which permits delivery of up to 0.5 mL of the reconstituted solution.

PHARMACOLOGY

Pharmacodynamics

Alprostadil (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. 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

The pharmacokinetics of intravenously administered alprostadil has 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 or children and is not for use in newborns.

CAVERJECT should not be used in patients with penile implants.

PRECAUTIONS

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

2. 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.

3. 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.

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

5. The injection of CAVERJECT can induce a small amount of bleeding at the site of injection (see Adverse Reactions). 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.*

USE IN PREGNANCY

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

Not applicable.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

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 with alprostadil. Limited data are available to assess the mutagenic potential of this formulation. Long term carcinogenicity studies have not been performed with this formulation.

$PGE_{1,}$ at doses up to 0.2 mg/kg/day SC, does not adversely affect or alter rat spermatogenesis.

DRUG INTERACTIONS

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 the intracavernosal injection.

ADVERSE REACTIONS

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 pain in the penis 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 conducted on the frequency of penile fibrosis was shown to be 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.

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

Body system	Adverse Events
Body as a whole	non-generalised weakness diaphoresis localised pain (buttocks, leg, genital, back or pelvic) leg cramps numbness yeast infection hyperaesthesia venous leak perineal pain
Reproductive, male	scrotal oedema scrotal disorder (redness, pain, spermatocele) testicular disorder (pain, warmth, swelling, mass, thickening) hemosiderin deposits in the penis painful erection abnormal ejaculation penile deviations penile warmth balanitis priapism phimosis
Urinary	haematuria urinary frequency, urgency or impaired urination increased serum creatinine urethral bleeding
Cardiovascular	cardiac arrhythmias postural hypotension changes in blood pressure supraventricular extrasystoles peripheral vascular disorder vagal shock vasovagal reactions
Central & peripheral nervous	collapse dizziness headache
Vision	mydriasis
Autonomic Nervous	vasodilatation
Skin & Appendages	rash erythema pruritus sensitivity irritation non-application site pruritus injection site haemorrhage injection site inflammation injection site oedema injection site itching or swelling
Gastrointestinal	nausea dry mouth

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.

The majority of patients obtain a satisfactory response with doses in the range of 10-20 micrograms. The maximum recommended frequency of injection is no more than once in a 24 hour period and no more than three times weekly.

CAVERJECT is administered by direct intracavernosal injection. The first injection of CAVERJECT must be given 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 specialist 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) Needle breakage, with a portion of the needle remaining in the penis, has been reported and, in some cases, required hospitalisation and surgical removal. The patient should be cautioned against using needles which are bent to inject CAVERJECT or attempting to straighten a bent needle prior to injecting.

(b) Instructions for the patient on how to use CAVERJECT Impulse are provided in each pack. The instructions are a summary of the procedure for self-injection with CAVERJECT Impulse and are intended only to support the instruction provided by medically qualified personnel after a patient has been assessed as competent to manage the procedure.

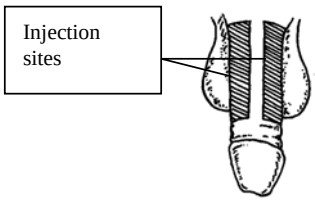
(c) The CAVERJECT Impulse device is designed for single use in one patient only and should be discarded after use regardless of the dose given and any solution that may be left in the cartridge. The patient should be instructed regarding appropriate injection technique and disposal of the syringe and needle after each injection.

General Procedure for Injection

CAVERJECT Impulse should be used as follows:

1. **Connect the needle to the device**
   - Remove all pieces from the package.
   - Clean the rubber membrane at the tip of the syringe using one of the alcohol swabs provided.
   - Peel the foil from the needle cap.
   - Attach the needle to the device by pressing the needle on to the tip of the device and turning clockwise until it is firmly in place.
2. **Remove the outer protective cap**.
   - Hold the device with the needle pointing upwards.
   - The plunger rod is now in the extended position.
3. **Reconstituting the powder and liquid**
   - Turn the plunger rod until it stops. This automatically mixes the alprostadil powder and the diluent.
   - Invert the device twice in order to make sure that the solution becomes evenly mixed. The solution should be clear.
   - **DO NOT** use if it is cloudy or contains particles.
4. **Remove the inner protective cap**
   - Hold the device with the needle pointing upwards.
   - Carefully remove the inner protective cap from the needle.
   - **Do NOT use if the needle is bent.**
5. **Remove air from the device**
   - Keeping the device upright, press the plunger rod as far as it will go. A few drops will appear at the needle point and the solution will be free from bubbles.
6. **Dialling the right dose**
   - Turn the end of the plunger rod slowly to choose the right dose.
   - The number appearing in the window indicates the dose of the injection.
   - If you make a mistake, continue to turn the plunger rod until you reach the correct dose.
7. **Before inserting the needle**
   - Stretch the penis straight out with the foreskin retracted in uncircumcised men.
   - Clean the site with an alcohol swab.
8. **Inserting the needle**
   - Inject into either of the two corpora cavernosa, avoiding any visible veins
   - Inject at 90 degrees to the skin; push the plunger firmly.
   - **DO NOT** force the CAVERJECT Impulse liquid from the syringe.

- 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.
- The penis should be massaged to help the alprostadil spread through it.
- 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.



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.

INCOMPATIBILITIES

This product is not intended to be administered with other intracavernosal medications.

OVERDOSAGE

Overdose data is limited. The pharmacologic 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. 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 for advice on the management of an overdose.

PRESENTATION

The CAVERJECT Impulse dual chamber cartridge is assembled as a single unit in a disposable syringe device consisting of a front sleeve and finger-grip/plunger assembly. The syringe device is designed to deliver a single dose only.

CAVERJECT Impulse dual chamber syringe is available in two strengths, 10 and 20 micrograms. In order to increase dosage flexibility, each syringe is capable of delivering 25% dosage increments:

CAVERJECT Impulse 10 micrograms: 2.5, 5.0, 7.5, 10 micrograms

CAVERJECT Impulse 20 micrograms: 5.0, 10, 15, 20 micrograms

CAVERJECT Impulse is supplied in packs of 2. Each pack contains 2 x 29 G needles and four alcohol swabs.

STORAGE CONDITIONS

The following distribution and patient storage conditions are recommended. Do not freeze the reconstituted solution.

Recommended storage conditions:

Strength, (µg)	Distribution Storage Temperature	Patient Storage Temperature	After Reconstitution
10, 20	Below 25°C. Protect from moisture.	Below 25°C. Protect from moisture.	To reduce microbiological hazard use as soon as possible. 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 injection preserved with benzyl alcohol) should be used for reconstituting CAVERJECT Impulse.

SPONSOR

Pfizer Australia Pty Ltd
38-42 Wharf Road
West Ryde NSW 2114
Australia

For medical enquires call 1800 675 229

Approved by TGA: 12 October 2005

Date of most recent amendment: 6 May 2010