AUSTRALIAN PRODUCT INFORMATION – CAVERJECT® IMPULSE (ALPROSTADIL)

1. NAME OF THE MEDICINE

Alprostadil.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Caverject Impulse dual chamber syringe is available in two strengths, 10 and 20 micrograms. Each 0.5 mL cartridge delivers a maximum dose of 10 micrograms or 20 micrograms of alprostadil.

Excipient(s) with known effect

Each mL of reconstituted solution contains 8.9 mg/mL of benzyl alcohol.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for intracavernosal injection

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

Dosage

Before initiation of treatment with Caverject Impulse, 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.

Erectile dysfunction of neurogenic or psychogenic etiology

If the erectile dysfunction is known to be of neurogenic or psychogenic aetiology, the generally recommended initial dose of Caverject Impulse is 2.5 micrograms with subsequent upward titration of the dose in increments of 2.5 micrograms.

Erectile dysfunction of arteriogenic origin or due to other organic causes

If the erectile dysfunction is known to be of arteriogenic origin or due to other organic causes, the generally recommended initial dose of Caverject Impulse is 5 micrograms with subsequent upward titration of the dose in increments of 5 micrograms.

Caverject Impulse as an adjunct to the diagnosis of erectile dysfunction

If the aetiology of the erectile dysfunction is unknown or the Caverject Impulse is being used as an adjunct in the diagnosis of impotence, the generally recommended initial dose of Caverject Impulse 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.

Method of administration

Caverject Impulse is administered by direct intracavernosal injection.

The first injection of Caverject Impulse 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 Impulse 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 Impulse should be adjusted if needed.

Note: (a) Caverject Impulse 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) Instructions for the patient on how to use Caverject Impulse are provided in each pack and are also provided below. 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.

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.

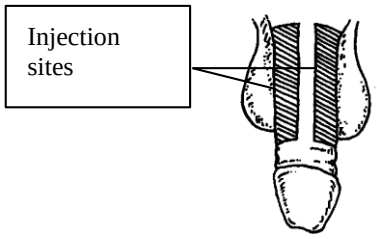
- If you make a mistake, continue to turn the plunger rod until you reach the correct dose.

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 Impulse should be halved for the next injection.

4.3 Contraindications

Intracavernosal alprostadil should not be used in patients who have a known hypersensitivity to alprostadil, the active ingredient in Caverject Impulse, 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 Impulse should not be used in patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis or Peyronie's disease.

Caverject Impulse should not be used in men for whom sexual activity is inadvisable or contraindicated. Caverject Impulse should not be used in women. It should not be used in children and is not for use in newborns (see Section 4.4 Special warnings and precautions for use).

Caverject Impulse should not be used in patients with penile implants.

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 Caverject Impulse.

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 Impulse. The occurrence of fibrosis may increase with increased duration of use of Caverject Impulse.

Patients should be carefully assessed for pre-existing penile fibrosis before initiation of treatment with intracavernosal Caverject Impulse. 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 Impulse 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 Impulse can induce a small amount of bleeding at the site of injection (see Section 4.8 Adverse effects (undesirable 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 Impulse 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 Impulse, and careful patient instruction in proper handling and injection techniques is required (see Section 4.2 Dose and method of administration).

Use in the elderly

No data available.

Paediatric use

Caverject Impulse should not be used in paediatric patients (see Section 4.3 Contraindications).

Effects on laboratory tests

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.5 Interactions with other medicines and other forms of interactions

No known interactions. Caverject Impulse 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 Impulse. The safety and efficacy of combinations of Caverject Impulse 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.

4.6 Fertility, pregnancy and lactation

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 Impulse should not be used in women (see Section 4.3 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 Impulse 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 Impulse with their obstetrician.

Use in lactation

Caverject Impulse should not be used in women (see Section 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

No data available.

4.8 Adverse effects (undesirable 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 Impulse 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 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

System Organ Class	Adverse Drug Reactions
	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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

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 with alprostadil. Limited data are available to assess the mutagenic potential of this formulation.

Carcinogenicity

Long term carcinogenicity studies have not been performed with this formulation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The front compartment contains:

- lactose monohydrate
- alfadex
- sodium citrate dihydrate
- hydrochloric acid solution and/or sodium hydroxide solution (used for pH adjustment).

The rear compartment contains:

- bacteriostatic Water for injections
- benzyl alcohol.

6.2 Incompatibilities

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

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Unreconstituted product

Store below 25°C. Protect from moisture.

Reconstituted solution

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 Injections preserved with benzyl alcohol) should be used for reconstituting Caverject Impulse.

6.5 Nature and contents of container

The Caverject Impulse dual chamber type 1 glass 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.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

The non-proprietary name is alprostadil, Prostaglandin E_1, (PGE_1) and the chemical name is (*11α*, 13*E*, 15*S*)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid. The molecular weight is 354.49.

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 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:

CAS number

745-65-3.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000.

Toll Free Number: 1800 675 229.
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

29 July 2002.

10. DATE OF REVISION

10 May 2019.

Summary Table of Changes

Section changed	Summary of new information
All	Reformatting according to new Australian PI template

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