NEW ZEALAND DATA SHEET

1. PRODUCT NAME

CAVERJECT® IMPULSE 10 and 20 microgram powder for injection

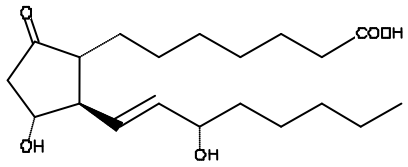
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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:

Chemical Structure



Excipient(s) with known effect

Each mL of reconstituted solution contains 8.04 mg of benzyl alcohol.

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

3. PHARMACEUTICAL FORM

Powder for Injection for intracavernous use.

Dual chamber glass cartridge containing a white lyophilised powder and diluent for reconstitution.

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

Dose

General information

Caverject Impulse is administered by direct intracavernosal injection. A 13 mm, 27 to 30 gauge, needle is recommended. The dose of Caverject Impulse should be individualised by careful titration under a physician's supervision.

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.

The first injections of Caverject Impulse 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 either dorso-lateral aspect of the proximal third of the penis. Visible veins should be avoided. Alternate which side of the penis is injected and vary the site of injection.

Reconstituted solutions of Caverject Impulse are intended for single use only; discard after use. Instruct the user in the proper disposal of the syringe and needle.

Erectile dysfunction of vasculogenic, psychogenic, or mixed etiology

Dosage titration should be initiated at 2.5 micrograms of alprostadil. If there is a partial response, the dose may be increased by 2.5 micrograms to a dose of 5 micrograms and then in increments of 5 to 10 micrograms, depending upon erectile response, until the dose that produces an erection suitable for intercourse and not exceeding one hour duration is reached. If there is no response to the initial 2.5 microgram dose, the second dose may be increased to 7.5 micrograms, followed by increments of 5 to 10 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 Impulse is 5 micrograms with subsequent upward titration of the dose in increments of 5 micrograms.

Erectile dysfunction of pure 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 microgram increments until the dose that produces an erection suitable for intercourse and not exceeding a duration of one hour is reached.

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.

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 Impulse. Extensions of this testing include the use of Caverject Impulse 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 Impulse that induces an erection with firm rigidity should be used.

Initial titration in physician's office

During dose titration, the patient must stay in the physician's office until complete detumescence occurs. If there is no response, the next higher dose may be given within one hour. If there is a response, allow at least a one-day interval before administering the next dose. The maximum recommended frequency of injection is no more than once in a 24 hour period and no more than three times weekly.

The majority of patients obtain a satisfactory response with doses in the range of 10-20 micrograms.

Maintenance therapy: self-injection

The dose of Caverject Impulse that is selected for self-injection treatment should provide the patient with an erection that is satisfactory for sexual intercourse and that is maintained for no longer than one hour. If the duration of erection is longer than one hour, the dose of Caverject Impulse should be reduced. Self-injection therapy for use at home should be initiated at the dose that was determined in the physician's office; however, if dose adjustment is required, it should be done only after consultation with the physician. The dose should be adjusted in accordance with the titration guidelines described above. The lowest effective dose should be employed. The recommended frequency of injection is no more than three times weekly with at least 24 hours between each dose. The patient may expect an erection to develop within 5 to 20 minutes.

The effectiveness of Caverject Impulse for long-term use of up to six months has been documented in an uncontrolled, self-injection study. The mean dose of alprostadil at the end of six months was 20.7 micrograms. In the majority of patients, the maintenance dose is between 5 micrograms and 20 micrograms. Maintenance doses of greater than 60 micrograms are not recommended.

Treatment monitoring recommendations

Regular follow-up is indicated while the patient is in the self-injection program. This is especially true for the initial self-injections, since adjustments in the dose of Caverject Impulse may be needed.

Paediatric population

Caverject Impulse should not be used in paediatric patients (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).

Method of Administration

Instructions to patients

(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. 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.

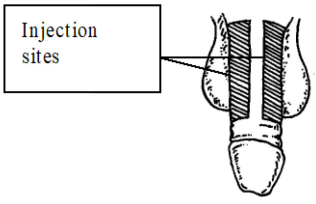
DO NOT force the Caverject Impulse liquid from the syringe.

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 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 paediatric patients (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 Undesirabel 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).

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

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

Fertility

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

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.

Lactation

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

4.7 Effects on ability to drive and use machinery

Alprostadil would not be expected to have an influence on the ability to drive or operate machinery.4.8 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 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 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:

Infections and infestations: Yeast infection.

Nervous system disorders: Vasovagal reaction, hyperaesthesia (systemic), penile numbness, decreased penile sensitivity, collapse, dizziness, headache.

Eye disorders: Mydriasis.

Cardiac disorders: Supraventricular extrasystoles, arrhythmia.

Vascular disorders: Hypotension, peripheral vascular disorder, vasodilatation, penile venous leak, vagal shock.

Skin and subcutaneous tissue disorders: Rash, pruritus, diaphoresis, erythema.

Musculoskeletal, connective tissue and bone disorders: Leg cramps, localised pain (buttocks, leg or back).

Gastrointestinal disorders: Nausea, dry mouth.

Renal and urinary disorders: Haematuria, urinary frequency, urinary urgency, urination impaired, urethral bleeding.

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, penile irritation, penile warmth, halanitis, priapism, pelvic pain, perineal pain, genital pain, phimosis.

General disorders and administration site conditions: Injection site haemorrhage, injection site inflammation, injection site oedema, injection site pruritus, injection site swelling, localised muscle weakness.

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Drugs used in erectile dysfunction. **ATC code:** G04B E01.

5.1 Pharmacodynamic properties

Pharmacodynamic effects

Alprostadil (Prostaglandin E_1 (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.

5.2 Pharmacokinetic properties

The pharmacokinetics of intravenously administered alprostadil has been extensively studied.

Absorption

For the treatment of erectile dysfunction, alprostadil is administered by injection into the corpora cavernosa.

Distribution

Following intracavernosal injection of 20 micrograms alprostadil, mean plasma concentrations of alprostadil increased 22 fold from the baseline endogenous levels approximately 5 minutes post-injection. Alprostadil concentrations then returned to endogenous levels within 2 hours after injection. Alprostadil is bound in plasma primarily to albumin (81% bound) and to a lesser extent α-globulin IV-4 fraction (55% bound). No significant binding to erythrocytes or white blood cells was observed.prior to excretion.

Metabolism

When administered intravenously to man, alprostadil is rapidly transformed to relatively inactive metabolites. 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.

Elimination

The metabolites of alprostadil are excreted primarily by the kidney, with almost 90% of an administered intravenous dose excreted in urine within 24 hours. The remainder of the dose

is excreted in the faeces. There is no evidence of tissue retention of alprostadil or its metabolites following intravenous administration. 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.

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 PARTICUALRS

6.1 List of excipients

Lyophilised power: Lactose monohydrate, sodium citrate dihyrate, α-cyclodextrin, hydrochloric acid for pH adjustment, sodium hydroxide for pH adjustment.

Diluent: Water for Injections preserved with benzyl alcohol.

6.2 Incompatibilities

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

6.3 Shelf life

3 years at store below 25^{o}C.

Reconstituted solution

To reduce microbiological hazard use the reconstituted solution 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.

6.4 Special precautions for storage

For storage conditions after reconstitution of the medicine, see Section 6.3 Shelf life.

6.5 Nature and contents of container

The 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 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. The rear compartment contains 0.6 mL of bacteriostatic Water for Injections (Water for Injections preserved with benzyl alcohol) which permits delivery of up to 0.5 mL of the reconstituted solution.

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

6.6 Special precautions for disposal

The syringe device is designed to deliver a single dose only. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand.

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

21 November 2013.

10. DATE OF REVISION OF THE TEXT

15 January 2019.

Summary table of changes (15 Jan 2019)

Section changed	Summary of new information
All	Change to SPC format

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