SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Caverject 10 micrograms
Caverject 20 micrograms

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alprostadil 10 micrograms.
When reconstituted, each 1ml delivers a dose of 10 micrograms of alprostadil.

Alprostadil 20 micrograms.
When reconstituted, each 1ml delivers a dose of 20 micrograms of alprostadil.
Alprostadil 10 micrograms & 20 micrograms:
Excipient with known effect:
Each 1ml of reconstituted solution contains 8.4 mg of benzyl alcohol, equivalent to 8.4 mg/ml.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Solution for Injection

A white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Caverject is indicated for the treatment of erectile dysfunction in adult males, due to neurogenic, vasculogenic, psychogenic or mixed aetiology.

Caverject may be a useful adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

4.2 Posology and method of administration

Caverject is administered by direct intracavernous injection. A half inch, 27 to 30 gauge needle is generally recommended. The dose of Caverject should be individualised for each patient by careful titration under supervision by a physician.

The intracavernosal injection must be done under sterile conditions. The site of injection is usually along the dorsolateral aspect of the proximal third of the penis. Visible veins should be avoided. Both the side of the penis that is injected and the site of injection must

be alternated; prior to the injection, the injection site must be cleansed with an alcohol swab.

To reconstitute Caverject using the prefilled diluent syringe: flip off the plastic cap from the vial, and use one of the swabs to wipe the rubber cap. Fit the 22 gauge needle to the syringe.

Inject the 1 ml of diluent into the vial, and shake to dissolve the powder entirely. Withdraw slightly more than the required dose of Caverject solution, remove the 22 gauge needle, and fit the 30 gauge needle. Adjust volume to the required dose for injection. Following administration, any unused contents of the vial or syringe should be discarded.

A. As an aid to aetiologic diagnosis.

i) Subjects without evidence of neurological dysfunction; 20 micrograms alprostadil to be injected into the corpus cavernosum and massaged through the penis. Should an ensuing erection persist for more than one hour detumescent therapy (please refer to section 4.9) should be employed prior to the subject leaving the clinic to prevent a risk of priapism.

Over 80% of subjects may be expected to respond to a single 20 micrograms dose of alprostadil. At the time of discharge from the clinic, the erection should have subsided entirely and the penis must be in a completely flaccid state.

ii) Subjects with evidence of neurological dysfunction; these patients can be expected to respond to lower doses of alprostadil. In subjects with erectile dysfunction caused by neurologic disease/trauma the dose for diagnostic testing must not exceed 10 micrograms and an initial dose of 5 micrograms is likely to be appropriate. Should an ensuing erection persist for more than one hour detumescent therapy (please refer to section 4.9) should be employed prior to the subject leaving the clinic to prevent a risk of priapism. At the time of discharge from the clinic, the erection should have subsided entirely and the penis must be in a completely flaccid state.

B. Treatment

The initial dose of alprostadil in patients with erectile dysfunction of neurogenic origin secondary to spinal cord injury is 1.25 micrograms, with a second dose of 2.5 micrograms, a third of 5 micrograms, and subsequent incremental increases of 5 micrograms until an optimal dose is achieved. For erectile dysfunction of vasculogenic, psychogenic, or mixed aetiology, the initial dose is 2.5 micrograms. The second dose should be 5 micrograms if there is a partial response, and 7.5 micrograms if there is no response. Subsequent incremental increases of 5-10 micrograms should be given until an optimal dose is achieved. If there is no response to the administered dose, then the next higher dose may be given within 1 hour. If there is a response, there should be at least a 1-day interval before the next dose is given. The usual maximum recommended frequency of injection is no more than once daily and no more than three times weekly.

The first injections of alprostadil must be done by medically trained personnel. After proper training and instruction, alprostadil may be injected at home. If self-administration is planned, the physician should make an assessment of the

patient's skill and competence with the procedure. It is recommended that patients are regularly monitored (e.g. every 3 months) particularly in the initial stages of self injection therapy when dose adjustments may be needed.
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 produces a duration of the erection not exceeding one hour. If the duration is longer, the dose should be reduced. The majority of patients achieve a satisfactory response with doses in the range of 5 to 20 micrograms. Doses of greater than 60 micrograms of alprostadil are not recommended. The lowest effective dose should be used.
Paediatric population:
Caverject is not indicated for paediatric use (see section 4.4 Benzyl alcohol).

4.3 Contraindications

Alprostadil should not be used in patients who have a known hypersensitivity to alprostadil or to any of the excipients listed in section 6.1; in patients who have conditions that might predispose them to priapism, such as sickle cell anaemia or trait, multiple myeloma, or leukaemia; or in patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease. Patients with penile implants should not be treated with alprostadil.

Alprostadil should not be used in men for whom sexual activity is inadvisable or contraindicated.

4.4 Special warnings and precautions for use

Prolonged erection and/or priapism may occur following intracavernosal administration of alprostadil. To minimize the risk, select the lowest effective dose. Patients should be instructed to report immediately to a physician, or if unavailable to seek immediate medical assistance for any erection lasting for a prolonged time period, such as 4 hours. Treatment of priapism should not be delayed more than 6 hours (please refer to section 4.9) and should be according to established medical practice.

Painful erection is more likely to occur in patients with anatomical deformations of the penis, such as angulation, phimosis, cavernosal fibrosis, Peyronie's disease or plaques. Penile fibrosis, including angulation, cavernosal fibrosis, fibrotic nodules and Peyronie's disease may occur following the intracavernosal administration of alprostadil. The occurrence of fibrosis may increase with increased duration of use. Regular follow-up of patients, with careful examination of the penis, is strongly recommended to detect signs of penile fibrosis or Peyronie's disease. Treatment with alprostadil should be discontinued in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease.

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

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

Use of intracavernosal alprostadil offers no protection from the transmission of sexually transmitted diseases. Individuals who use alprostadil should be counselled about the protective measures that are necessary to guard against the spread of sexually transmitted diseases, including the human immunodeficiency virus (HIV). In some patients, injection of alprostadil can induce a small amount of bleeding at the site of injection. In patients infected with blood-borne diseases, this could increase the transmission of such diseases to their partner.

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

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

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

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

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; they should also not attempt to straighten a bent needle. They should remove the needle from the syringe, discard it, and attach a new, unused sterile needle to the syringe.

Reconstituted solutions of alprostadil are intended for single use only, they should be used immediately and not stored. The syringe and any remaining solution should be properly discarded.

Excipient information

Benzyl alcohol

Caverject contains benzyl alcohol, which may cause hypersensitivity reactions.
The combined daily metabolic load of benzyl alcohol from all sources should be considered, especially in patients with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).
This medicine is only indicated for intracavernosal injection. Intravenous administration of the preservative benzyl alcohol has been associated with serious adverse events, and death in paediatric patients including neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known.

Premature and low-birth weight infants may be more likely to develop toxicity. Caverject is not indicated for paediatric use.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Sympathomimetics may reduce the effect of alprostadil. Alprostadil may enhance the effects of antihypertensives, vasodilative agents, anticoagulants and platelet aggregation inhibitors.

4.6 Fertility, pregnancy and lactation

Not applicable.
High doses of alprostadil (0.5 to 2.0 mg/kg subcutaneously) had an adverse effect on the reproductive potential of male rats, although this was not seen with lower doses (0.05 to 0.2 mg/kg). Alprostadil did not affect rat spermatogenesis at doses 200 times greater than the proposed human intrapenile dose.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequent adverse reaction after intracavernosal injection of alprostadil is penile pain. Thirty percent of the patients reported penile pain at least once; however, this event was associated with only 11% of the administered injections. In the majority of the cases, penile pain was rated mild or moderate in intensity. 3% of patients discontinued treatment because of penile pain.

Prolonged erection (defined as an erection that lasts for 4 to 6 hours) after intracavernosal administration of alprostadil 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.

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

Haematoma and ecchymosis at the site of injection, which is related to the injection technique rather than to the effects of alprostadil, occurred in 3% and 2% of patients, respectively. Penile oedema or rash was reported by 1% of alprostadil treated patients.

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

System Organ Class	Frequency	Undesirable effects
Infections and Infestations	Uncommon	Fungal infection, Common cold
Nervous System Disorders	Uncommon	Presyncope, Hypoaesthesia, Hyperaesthesia
	Not known	Cerebrovascular accident
Eye Disorders	Uncommon	Mydriasis
Cardiac Disorders	Uncommon	Supraventricular extrasystoles
	Not known	Myocardial ischaemia
Vascular Disorders	Uncommon	Venous haemorrhage, Hypotension, Vasodilatation, Peripheral vascular disorder, Vein disorder
Gastrointestinal Disorders	Uncommon	Nausea, Dry mouth
Skin and Subcutaneous Tissue Disorders	Uncommon	Erythema, Rash, Hyperhidrosis, Pruritus
Musculoskeletal and Connective Tissue Disorders	Common	Muscle spasms
Renal and Urinary Disorders	Uncommon	Urethral haemorrhage, Haematuria, Dysuria, Pollakiuria, Micturition urgency
Reproductive System and Breast Disorders	Very common	Penile pain
	Common	Peyronie's disease, Penis disorder, Erection increased
	Uncommon	Priapism, Pelvic pain, Testicular mass, Spermatocele, Testicular swelling, Testicular oedema, Testicular disorder, Scrotal pain, Scrotal erythema, Scrotal oedema, Testicular pain, Scrotal disorder, Painful erection, Balanitis, Phimosis, Erectile dysfunction, Ejaculation disorder
General Disorders and Administration Site Conditions	Common	Injection site haematoma, Haematoma, Ecchymosis
	Uncommon	Haemorrhage, Injection site haemorrhage, Inflammation, Injection site inflammation, Injection site warmth, Injection site oedema, Injection site swelling, Injection site pain, Injection site irritation, Asthenia, Injection site anaesthesia, Oedema, Oedema peripheral, Injection site pruritus
Investigations	Uncommon	Blood creatinine increased, Blood pressure decreased, Heart rate increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

The pharmacotoxic signs of alprostadil are similar in all animal species and include depression, soft stools or diarrhoea and rapid breathing. In animals, the lowest acute LD_{50} was 12 mg/kg which is 12,000 times greater than the maximum recommended human dose of 60 micrograms.

In man, prolonged erection and/or priapism are known to occur following intracavernous 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.

Overdosage was not observed in clinical trials with alprostadil. If intracavernous overdose of alprostadil occurs, the patient should be placed under medical supervision until any systemic effects have resolved and/or until penile detumescence has occurred. Symptomatic treatment of any systemic symptoms would be appropriate.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction

ATC code: G04B E01

Alprostadil is present in various mammalian tissues and fluids. It has a diverse pharmacologic profile, among which some of its more important effects are vasodilation, inhibition of platelet aggregation, inhibition of gastric secretion, and stimulation of intestinal and uterine smooth muscle. The pharmacologic effect of alprostadil in the treatment of erectile dysfunction is presumed to be mediated by inhibition of $alpha_1$-adrenergic activity in penile tissue and by its relaxing effect on cavernosal smooth muscle.

5.2 Pharmacokinetic properties

Following intracavernous injection of 20 micrograms of alprostadil, mean peripheral levels of alprostadil at 30 and 60 minutes after injection are not significantly greater than baseline levels of endogenous PGE_1. Peripheral levels of the major circulating metabolite, 15-oxo-13,14-dihydro-PGE_1, increase to reach a peak 30 minutes after injection and return to pre-dose levels by 60 minutes after injection. Any alprostadil entering the systemic circulation from the corpus cavernosum will be rapidly metabolised. Following intravenous administration, approximately 80% of the circulating alprostadil is metabolised in one pass through the lungs, primarily by beta- and omega-oxidation. The metabolites are excreted primarily by the kidney and excretion is essentially complete within 24 hours. There is no evidence of tissue retention of alprostadil or its metabolites following intravenous administration.

5.3 Preclinical safety data

No relevant information additional to that already contained in this SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

powder vial:
alpha cyclodextrine
lactose monohydrate
sodium citrate

hydrochloric acid for pH adjustment
sodium hydroxide for pH adjustment

Diluent:
benzyl alcohol (8.4 mg not including 5% overage)
water for injection

6.2 Incompatibilities

Caverject is not intended to be mixed or coadministered with any other products.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.. Reconstituted solutions should be used immediately and not stored.

6.4 Special precautions for storage

Store below 25ºC. Reconstituted solutions are intended for single use only, they should be used immediately and not stored.

6.5 Nature and contents of container

Single pack containing a 5 ml clear, colourless, glass vial of Caverject 10 micrograms or Caverject 20 micrograms powder with a bromobutyl rubber stopper and an aluminium overseal with polypropylene flip-off cap.

Packs also each contain a syringe of solvent, a sterile 22G and a 30G needle plus pre-injection swab.

6.6 Special precautions for disposal

The presence of benzyl alcohol in the reconstitution vehicle decreases the degree of binding to package surfaces. Therefore, a more consistent product delivery is produced when Bacteriostatic Water for Injection containing benzyl alcohol is used.

Use immediately after reconstitution.

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., 46725 Herzliya Pituach.

8. LICENSE NUMBER

Caverject 10 mcg: 101-08-28542
Caverject 20 mcg: 068-13-28275

Updated in 11/ 2021 according to MOH guidelines