

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Caverject Dual Chamber 20 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 ml cartridge delivers a maximum dose of 20 micrograms of alprostadil.

Excipients with known effect

Benzyl alcohol 8.9 mg/ml.

Sodium citrate, sodium hydroxide (sodium 0.034 mg/ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Caverject is not indicated for paediatric use (see section 4.4 Benzyl alcohol).

4.2 Posology and method of administration

Posology

No formal studies with Caverject have been performed in patients younger than 18 years and older than 75 years.

Method of administration

Caverject Dual Chamber should be administered by direct intracavernosal injection using the 1/2-inch 29 gauge needle provided. The usual site of injection is along the dorsolateral aspect of the proximal third of the penis. Visible veins should be avoided. Both the side of the penis and the site of injection must be altered between injections.

The initial injections of Caverject Dual Chamber must be administered by medically trained personnel and after proper training, alprostadil may be injected at home. 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 of Caverject Dual Chamber should be individualised for each patient by careful titration under a physician's supervision. The lowest effective dose should be used that provides 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.

The delivery device is designed to deliver a single dose which can be set at 25% increments of the nominal dose. Doses greater than 40 micrograms of alprostadil are not routinely justified. The following doses can be given using Caverject Dual Chamber:

<u>Presentation</u>	<u>Dose Available</u>
Caverject Dual Chamber 20 micrograms	5, 10, 15, 20 micrograms

Treatment

The initial dose of alprostadil for erectile dysfunction of vasculogenic, psychogenic, or mixed aetiology 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 to 10 micrograms should be given until an optimal dose is identified. If there is no response to the administered dose, then the next higher dose may be given within one hour. If there is a response, there should be a one day interval before the next dose is given.

For patients with erectile dysfunction of neurogenic origin requiring doses less than 2.5 micrograms, it should be considered to dose titrate with Caverject Powder for Injection. Starting with a dose of 1.25 micrograms, if this produces no response, the second dose should be 2.5 micrograms. Apart from the starting dose, it is possible to dose titrate with either Caverject Dual Chamber or Caverject Powder for Injection with similar increments to the treatment of non-neurogenic erectile dysfunction.

The maximum recommended frequency of injection is no more than once daily and no more than three times weekly.

Adjunct to aetiologic diagnosis

Patients without evidence of neurological dysfunction: 10 to 20 micrograms alprostadil to be injected into the corpus cavernosum and massaged through the penis. Over 80% of patients may be expected to respond to a single 20 micrograms dose of alprostadil.

Patients with evidence of neurological dysfunction: These patients can be expected to respond to lower doses of alprostadil. In patients 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 should be employed prior to the patient leaving the clinic to prevent a risk of priapism (see section 4.9). At the time of discharge from the clinic, the erection should have subsided entirely and the penis must be in a completely flaccid state.

In case of lack of erectile response during the titration phase, patients should be monitored for systemic adverse effects.

4.3 Contraindications

Caverject Dual Chamber must not be used in patients who have:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Conditions that might predispose them to priapism, such as sickle cell anaemia or trait, multiple myeloma, or leukaemia.
- Anatomical deformation of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease.
- Penile implants.

Caverject Dual Chamber must not be used in men for whom sexual activity is contraindicated (e.g. patients suffering from severe heart disease).

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 alprostadil.

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

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 Caverject Dual Chamber. 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 Caverject Dual Chamber 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. In some patients, injection of Caverject Dual Chamber 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.

Caverject should be used with caution in patients with cardiovascular and cerebrovascular risk factors.

Caverject should be used with care 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. Caverject should be used with care in these patients and they should engage in sexual activity with caution.

Caverject Dual Chamber is not intended for co-administration with any other agent for the treatment of erectile dysfunction (see section 4.5).

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

Reconstituted solutions of Caverject Dual Chamber are intended for single use only. The injection delivery system/syringe and any remaining solution should be properly discarded.

Caverject Dual Chamber 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.

Benzyl alcohol

Caverject Dual Chamber 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 Dual Chamber is not indicated for paediatric use.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Sympathomimetics may reduce the effect of alprostadil.

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

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

4.6 Fertility, pregnancy and lactation

Not applicable.

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

Summary of the safety profile

The most frequent adverse effect following an intracavernous injection was pain in the penis. Thirty percent of patients reported pain at least once. Pain was associated with 11% of the injections administered. In most cases pain was assessed as mild or moderate. Three per cent of patients discontinued treatment because of pain.

Penile fibrosis, including angulation, fibrotic nodules, and Peyronie's disease, was reported in 3% of clinical trial patients overall. 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 injection site, which is related with the injection technique rather than the effect of alprostadil, was reported by 3% and 2% of patients, respectively.

Prolonged erection (an erection for 4 to 6 hours) developed in 4% of patients. Priapism (a painful erection for more than 6 hours) occurred in 0.4%. In most cases it disappeared spontaneously.

Tabulated list of adverse reactions

Adverse drug reactions reported during clinical trials and post marketing experience are presented in the table below, frequencies are very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ 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	Very common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$	Not known (cannot be estimated from the available data)
Infections and infestations			Fungal infection, Common cold	

System Organ Class	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)
Nervous system disorders			Presyncope, Hypoaesthesia, Hyperaesthesia	Cerebrovascular accident
Eye disorders			Mydriasis	
Cardiac disorders			Supraventricular extrasystoles	Myocardial ischaemia
Vascular disorders			Venous haemorrhage, Hypotension, Vasodilatation, Peripheral vascular disorder, Vein disorder	
Gastrointestinal disorders			Nausea, Dry mouth	
Skin and subcutaneous tissue disorders			Rash, Hyperhidrosis, Pruritus, Erythema	
Musculoskeletal and connective tissue disorders		Muscle spasms		
Renal and urinary disorders			Urethral haemorrhage, Haematuria, Dysuria, Pollakiuria, Micturition urgency	
Reproductive system and breast disorders	Penile pain	Peyronie's disease, Penis disorders (including penile fibrosis, angulation and fibrotic nodules), Erection increased	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	

System Organ Class	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)
General disorders and administration site conditions		Injection site haematoma, Ecchymosis	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			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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdosage was not observed in clinical trials with alprostadil. If intracavernous overdose of Caverject Dual Chamber 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 to 21 gauge butterfly needle into the corpus cavernosum and aspirate 20 to 50 ml of blood. This may detumescence 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 contraindication 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 patients 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 epinephrine 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 epinephrine 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 the naturally occurring form of prostaglandin E₁ (PGE₁). Alprostadil has a wide variety of pharmacological actions; vasodilation and inhibition of platelet aggregation are among the most notable of these effects. In most animal species tested, alprostadil relaxed 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 phenylephrine or PGF_{2α} *in vitro*. 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 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 the venules against the tunica albuginea, a process referred to as the corporal veno-occlusive mechanism. Erection usually occurs 5 to 15 minutes after injection. Its duration is dose dependent.

5.2 Pharmacokinetic properties

Caverject Dual Chamber contains alprostadil as the active ingredient in a complex with alfadex. At reconstitution, the complex is immediately dissociated into alprostadil and alfadex. The pharmacokinetics of alprostadil is therefore unchanged in Caverject Dual Chamber in comparison with Caverject Powder for Injection.

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.

Biotransformation

Alprostadil is rapidly converted to compounds that are further metabolised prior to excretion. Following intravenous administration, approximately 80% of circulating alprostadil is metabolised in one pass through the lungs, primarily by beta- and omega-oxidation. Hence, any alprostadil entering the systemic circulation following intracavernosal injection is rapidly metabolized. The primary metabolites of alprostadil are 15-keto-PGE₁, 15-keto-13,14-dihydro-PGE₁, and 13,14-dihydro-PGE₁. In contrast to

15-keto-PGE₁ and 15-keto-13,14-dihydro-PGE₁, which lack almost completely biological activity, 13,14-dihydro-PGE₁ has been shown to lower blood pressure and inhibit platelet aggregation. Plasma concentrations of the major circulating metabolite (15-keto-13,14-dihydro-PGE₁) increased 34 fold from the baseline endogenous levels 10 minutes after the injection and returned to baseline levels 2 hours post-injection. Plasma concentrations of 13,14-dihydro-PGE₁ increased 7 fold, 20 minutes after injection.

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 volunteers, 70% to 90% of alprostadil is extensively extracted and metabolised in a single pass through the lungs, resulting in a short elimination half-life of less than one minute.

Renal or hepatic impairment

Pulmonary first-pass metabolism is the primary factor influencing the systemic clearance of alprostadil. Although the pharmacokinetics of alprostadil have not been formally examined in patients with renal or hepatic impairment, alterations in renal or hepatic function would not be expected to have a major influence on the pharmacokinetics of alprostadil.

5.3 Preclinical safety data

Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Alprostadil at subcutaneous doses of up to 0.2 mg/kg/day had no adverse effect on the reproductive function in male rats.

A standard battery of genotoxicity studies revealed no mutagenic potential of alprostadil or alprostadil/alfadex.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Caverject Dual Chamber powder:	Lactose monohydrate Sodium citrate Alfadex Hydrochloric acid (for pH-adjustment) Sodium hydroxide (for pH-adjustment)
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Diluent:	Benzyl alcohol Water for injections
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6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the medicinal product as packaged for sale
36 months.

Shelf life of the medicinal product after reconstitution

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Two or ten*, Type I, Ph. Eur, clear, borosilicate glass cartridges divided into two compartments and sealed with a bromobutyl rubber plunger. The cartridge is sealed with an aluminium cap containing a bromobutyl rubber disc.

Two or ten* 29 G injection needles.

Four or twenty *, pouches containing isopropyl cleansing tissues.

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use

To perform the reconstitution, attach the needle to the device by pressing the needle onto the tip of the device and turning clockwise until it stops. Remove the outer protective cap of the needle. Turn the plunger rod clockwise until it stops to reconstitute the alprostadil powder. Invert the device twice in order to make sure the solution is evenly mixed. The solution should be clear. Carefully remove the inner protective cap from the needle. Holding the device upright, press the plunger rod as far as it will go. A few drops will appear at the needle tip. Turn the end of the plunger rod clockwise to select the desired dose.

The package insert provides full instructions on reconstitution, cleansing of the injection site, and also how to perform the injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
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Sandwich
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CT13 9NJ
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8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/0940

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

13/07/2010

10 DATE OF REVISION OF THE TEXT

08/03/2019