CAVERJECT®

Alprostadil
10 micrograms and 20 micrograms Powder for Injection

PRESENTATION

Caverject is a white crystalline powder containing 10 micrograms or 20 micrograms alprostadil in a 5 mL clear glass vial.

USES

Actions

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 noradrenaline or PGF₂α 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.

Pharmacokinetics

Absorption

For the treatment of erectile dysfunction, alprostadil is administered by injection into the corpora cavernosa. The absolute bioavailability of alprostadil has not been determined.

Distribution

Following intracavernosal injection of 20 micrograms alprostadil, mean peripheral plasma concentrations of alprostadil at 30 and 60 minutes after injection (89 and 102 picograms/mL, respectively) were not significantly greater than baseline levels of endogenous alprostadil (96 picograms/mL). 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 or Metabolism

Alprostadil is rapidly converted to compounds which 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 very rapidly metabolised. 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. Following intravenous or intra-arterial administration of alprostadil, levels of this metabolite were in the same order of magnitude as those of PGE₁, while levels of 15-keto-13,14-dihydro-PGE₁, the major circulating metabolite, were more than 10-fold higher. Plasma 15-keto-PGE₁ remained undetectable throughout the observation period. Following intracavernosal injection of 20 μg alprostadil, peripheral levels of the major circulating metabolite, 13,14-dihydro-15-oxo-PGE₁, increased to reach a peak 30 minutes after injection and returned to pre-dose levels by 60 minutes after injection while peripheral levels of alprostadil were not significantly greater than baseline levels. Plasma concentrations of 13,14-dihydro-PGE₁ were not determined.

**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 post-dose. 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.

**Effect on Race**

The potential effect of race on the pharmacokinetics of alprostadil following intracavernous use has not been evaluated.

**Use in the Elderly**

The potential effect of age on the pharmacokinetics of alprostadil following intracavernous use has not been evaluated.

**Use in the Renal Disease**

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 insufficiency, alterations in renal function would not be expected to have a major influence on the pharmacokinetics of alprostadil.

**Use in Hepatic Disease**

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 hepatic insufficiency, alterations in hepatic function would not be expected to have a major influence on the pharmacokinetics of alprostadil.

**INDICATIONS**

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

**DOSAGE AND ADMINISTRATION**

**General Information**

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

The first injections of Caverject 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 are intended for single use only; discard after use. Instruct the user in the proper disposal of the syringe, needles, and vial.

**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.

**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 a duration of one hour 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.

**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.

**Maintenance Therapy: Self-Injection**

The dose of Caverject 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 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 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.

**Caverject as an Adjunct to the Diagnosis of Erectile Dysfunction**

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. Extensions of this testing include the use of Caverject as an adjunct to laboratory investigations, such as duplex or Doppler imaging, $^{133}$Xenon washout tests, radioisotope penogram, and penile arteriography, to allow visualisation and assessment of penile vasculature. For any of these tests, a single dose of Caverject that induces an erection with firm rigidity should be used.

**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 may be needed.

**Instructions to Patients**

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; 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.

**CONTRAINDICATIONS**

Caverject is contraindicated in the following patients:

- patients who have a known hypersensitivity to alprostadil or any component of Caverject
- patients who have conditions that might predispose them to priapism, such as sickle cell anaemia or trait, multiple myeloma, or leukaemia
- patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease
- patients with penile implants
• patients for whom sexual activity is inadvisable or contraindicated
• women
• children and newborns (see Warnings and Precautions).

WARNINGS AND PRECAUTIONS

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

Priapism (erection lasting over six hours) may occur following intracavernosal administration of Caverject. To minimise the risk select the lowest effective dose and instruct patients to immediately consult with their physician and seek medical assistance for any prolonged erection lasting more than 4 hours. Treatment of priapism should be according to established medical practice.

Penile fibrosis, including angulation, fibrotic nodules, and Peyronie's disease, may occur following the intracavernosal administration of Caverject. The occurrence of fibrosis may increase with increased duration of use of Caverject. Regularly scheduled follow-up and examination of the penis to detect signs of penile fibrosis or Peyronie's disease is strongly recommended. Treatment with Caverject should be discontinued in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease.

Because a small amount of bleeding may occur at the injection site patients should be counselled about the protective measures that are necessary to guard against the spread of sexually transmitted diseases, including HIV, and blood-borne diseases. Patients on anticoagulants, such as warfarin or heparin, may have increased propensity for bleeding after intracavernosal injection.

The possibility of needle breakage exists with Caverject, and careful patient instruction in proper handling and injection techniques is required (see Dosage and Administration).

CHO/HGPRT mammalian cell forward gene mutation and unscheduled DNA synthesis (UDS).

The bacteriostatic Water for Injections provided with Caverject contains benzyl alcohol, which is associated with severe adverse effects including fatal “gloppy 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.

Effect on Fertility
Rat reproductive studies indicate that subcutaneous doses of alprostadil of up to 2.0 mg/kg/day does not adversely affect or alter rat spermatogenesis.

Use in Pregnancy
Caverject should not be used in women (see Contraindications). Alprostadil is an abortifacient and stimulates uterine smooth muscle. Since PGE₁ occurs naturally in seminal
fluid at doses greater than would be achieved if the Caverject were inadvertently injected into
the urethra the injected alprostadil would not significantly increase the activity of the
endogenous PGE1. However, patients should be advised that pregnant partners should
discuss the use of Caverject with their obstetrician.

Use in Lactation
Caverject should not be used in women (see Contraindications).

Paediatric Use
Caverject should not be used in paediatric patients (see Contraindications).

Genotoxicity
The following battery of mutagenicity assays revealed no potential for mutagenesis: bacterial
mutation (Ames), alkaline elution, rat micronucleus, sister chromatid exchange.

Carcinogenicity
Long-term carcinogenicity studies have not been conducted.

Effects on Ability to Drive and Use Machines
None known.

ADVERSE EFFECTS

The most frequent adverse reaction after intracavernosal injection of Caverject is mild to
moderate penile pain reported in approximately 11% of self-injections by men in clinical
studies. It was reported at least once by about one third of all patients, although only 3%
discontinued use for this reason. Penile fibrosis (including Peyronie's disease, angulation,
and fibrotic nodules), 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 approximately 8% (see Warnings and Precautions).

Hematoma and ecchymosis at the site of injection, which are related to the injection
technique rather than to the effects of Caverject, occurred in 3% and 2% of patients,
respectively. Prolonged erection (defined as an erection that lasts for four to six hours) after
intracavernosal administration of Caverject was reported in 4% of patients. The frequency of
priapism (defined as an erection that lasts six hours or longer) was 0.4% (see Warnings and
Precautions). In the majority of cases, spontaneous detumescence occurred.

Haemodynamic changes, manifested as decreases in blood pressure at doses greater than
20 micrograms and increases in pulse rate at doses greater than 30 micrograms, were
observed during clinical studies and appeared to be dose-dependent. However these changes
were usually clinically unimportant; only three patients discontinued the treatment because of
symptomatic hypotension.

Caverject had no clinically important effect on serum or urine laboratory tests.

Adverse reactions reported by less than 1% of patients in clinical studies are listed in the table
below:
<table>
<thead>
<tr>
<th><strong>Body system</strong></th>
<th><strong>Adverse Drug Reactions</strong></th>
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</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Yeast infection</td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>Scrotal oedema</td>
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<td></td>
<td>Scrotal disorder (redness, pain, spermatocele)</td>
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<tr>
<td></td>
<td>Testicular disorder (warmth, swelling, mass, thickening)</td>
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<td></td>
<td>Testicular pain</td>
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<td></td>
<td>Haemosiderin deposits in the penis</td>
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<td></td>
<td>Painful erection</td>
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<td>Ejaculation abnormal</td>
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<td>Penile deviations</td>
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<td>Penile irritation</td>
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<td>Penile warmth</td>
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<td>Balanitis</td>
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<td>Priapism</td>
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<td>Pelvic pain</td>
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<td>Perineal pain</td>
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<td>Genital pain</td>
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<td>Phimosis</td>
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<td>Renal and urinary disorders</td>
<td>Haematuria</td>
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<td>Urinary frequency</td>
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<td>Urinary urgency</td>
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<td>Urination impaired</td>
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<td>Urethral bleeding</td>
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<td>Cardiac disorders</td>
<td>Supraventricular extrasystoles</td>
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<td>Arrhythmia</td>
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<td>Vascular disorders</td>
<td>Hypotension</td>
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<td>Peripheral vascular disorder</td>
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<td>Vasodilatation</td>
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<td>Penile venous leak</td>
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<td>Vagal shock</td>
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<tr>
<td>Nervous system disorders</td>
<td>Vasovagal reaction</td>
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<td></td>
<td>Hyperaesthesia (systemic)</td>
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<td>Penile numbness</td>
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<td>Decreased penile sensitivity</td>
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<td>Collapse</td>
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<td>Dizziness</td>
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<td>Headache</td>
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<td>Eye disorders</td>
<td>Mydriasis</td>
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<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
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<td>Pruritus</td>
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<td></td>
<td>Diaphoresis</td>
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<td>Erythema</td>
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<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Leg cramps</td>
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<td></td>
<td>Localised pain (buttocks, leg or back)</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site haemorrhage</td>
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<td></td>
<td>Injection site inflammation</td>
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Version: pfdcavev10416
Supersedes: pfdcavev10915
Page 7 of 10
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<td>Localised muscle weakness</td>
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<td>Gastrointestinal disorders</td>
<td>Nausea</td>
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<td>Dry mouth</td>
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<td>Investigations</td>
<td>Blood creatinine increased</td>
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<td>Changes in blood pressure</td>
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</table>

In some patients, these adverse events may be related to the injection procedure rather than to the pharmacological effects of alprostadil.

**INTERACTIONS**

The potential for pharmacokinetic drug-drug interactions between Caverject and other agents has not been formally studied. In clinical trials, concomitant use of agents such as antihypertensive drugs, diuretics, antidiabetic agents (including insulin), or non-steroidal anti-inflammatory drugs had no effect on the safety or efficacy of Caverject. The safety and efficacy of combinations of Caverject and other vasoactive agents have not been systematically studied.

**OVERDOSAGE**

Overdose data is limited. The pharmacologic signs of alprostadil are similar in all animal species and include depression, soft stool or diarrhoea and rapid breathing.

In man, prolonged erection and/or priapism are known to occur following intracavernosal administration of vasoactive substances, including alprostadil. Patients should be instructed to report to a physician any erection lasting for a prolonged time period, such as 4 hours or longer. Prolonged erection or priapism (lasting more than 6 hours) should be treated to prevent tissue hypoxia and possible necrosis.

The treatment of priapism may include different approaches such as aspiration, intracavernosal injection of sympathomimetic amines or surgery.

There is no antidote for alprostadil overdose. Treatment is symptomatic and supportive. Support respiratory and cardiac function. Monitor pulmonary function, vital signs, ECG, pulse oximetry, and fluid and electrolyte status in patients with significant diarrhoea.

Contact the National Poisons Centre on 0800 764 766 for advice on the management of an overdose.
**PHARMACEUTICAL PRECAUTIONS**

**Instructions for Use/Handling**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit.

Bacteriostatic Water for Injections preserved with 9.45 mg/mL benzyl alcohol must be used for reconstitution of Caverject. After reconstitution with 1 mL of diluent, the volume of the resulting solution is 1.13 mL. Depending on vial strength, 1 mL of the reconstituted solution will contain either 10.5 or 20.5 micrograms of alprostadil. The deliverable amount of alprostadil is 10 or 20 micrograms/mL because approximately 0.5 micrograms is lost due to adsorption to the vial and syringe.

**Incompatibilities**

Only the accompanying bacteriostatic Water for Injections should be used when reconstituting Caverject.

**Shelf life**

Caverject should be stored at or below 25°C.

The reconstituted solution should be used immediately. The reconstituted solution should not be frozen.

**MEDICINE CLASSIFICATION**

Prescription Medicine.

**PACKAGE QUANTITIES**

Caverject containing 10 or 20 micrograms alprostadil is supplied in a pack of 1 5 mL glass vial with a 1 mL prefilled diluent (bacteriostatic Water for Injections preserved with benzyl alcohol) syringe, two needles (a 22 gauge needle for reconstitution and a 27 to 30 gauge needle for injection) and two swabs.

**FURTHER INFORMATION**

**Preclinical Data**

A 1-year irritancy study was conducted in Cynomolgus monkeys injected intracavernosally twice weekly with either vehicle or 3 or 8.25 micrograms of alprostadil per injection. Additional monkeys were injected as described previously plus they received multiple doses during weeks 44, 48, and 52. Monkeys from each group were retained for a 4-week recovery period. There was no evidence of drug-related penile irritancy or nonpenile tissue lesions, which could be directly related to alprostadil. The irritancy which was noted for control and treated monkeys was considered to be a result of the injection procedure itself, and any
lesions noted were shown to be reversible. At the end of the 4-week recovery period, the histological changes in the penis had regressed.

**Chemical Structure**

Alprostadil is a white to off-white crystalline powder with a melting point between 115°C - 116°C. Its solubility at 35°C is 8000 micrograms/100 mL double distilled water. The acid dissociation constant (Ka) is approximately 1.1 X 10⁻⁵. The chemical name is (11a,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid. Molecular weight is 354.49. The structural formula is as follows:

![Chemical Structure Diagram]

**Excipients**

Caverject Powder for Injection: Lactose monohydrate (diluent), α-cyclodextrine (stabiliser), sodium citrate dihydrate (pH buffer), hydrochloric acid solution 10% (adjust pH), sodium hydroxide solution (adjust pH), benzyl alcohol (preservative), Water for Injections (solvent).

**NAME AND ADDRESS**

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**DATE OF PREPARATION**

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