SCHEDULING STATUS:

S4

PROPRIETARY NAME (and dosage form):

CAVERJECT® 20 µg (Powder for injection)

COMPOSITION:

Each vial contains 20 micrograms alprostadil.
When reconstituted with 1 ml of the Bacteriostatic Water for Injection, each 1 ml contains: alprostadil 20 micrograms and benzyl alcohol 0,9 % m/v as preservative.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1 Vasodilators

PHARMACOLOGICAL ACTION:

Alprostadil (prostaglandin E_1, PGE_1) is one of a family of naturally-occurring acidic lipids, and is present in various mammalian tissues and fluids, including the semen of fertile men.
Alprostadil 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, thus, alprostadil induces erection by relaxation of the trabecular smooth muscle and by dilation of cavernosal arteries. This leads to expansion of the lacunar spaces and entrapment of blood by compressing venules against the tunica albuginea - a process referred to as the corporal veno-occlusive mechanism.
Alprostadil, when given by intracavernosal injection, induces an erection within 10 to 30 minutes after administration and the duration of erection is dose-dependant.

Pharmacokinetics:

Following intracavernosal injection of 20 µg 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.

INDICATIONS:

Treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic or mixed aetiology.

An adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.

CONTRA-INDICATIONS:

Intracavernosal alprostadil should not be used in patients who have a known hypersensitivity to alprostadil, benzyl alcohol, or any of the other constituents, or 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 deformity of the penis such as angulation, cavernosal fibrosis, or Peyronie's disease. Patients with a penile implant should not be treated with CAVERJECT.

CAVERJECT should not be used in men in whom sexual activity is medically inadvisable or contra-indicated.

CAVERJECT should not be used in women or children and is not for use in newborns.

WARNINGS:

Prolonged erection and/or priapism may occur. Patients should be instructed to report to a physician any erection lasting for a prolonged time period, such as 4 hours or longer. Treatment of priapism should be according to established medical practice (See KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

Penile fibrosis, including angulation, fibrotic nodules and Peyronie’s disease occurred in 3 % of patients in clinical studies with CAVERJECT. Regular follow-up of patients, with careful examination of the penis, is strongly recommended to detect signs of penile fibrosis. Treatment with CAVERJECT 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 CAVERJECT.

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). The injection of CAVERJECT can induce a small amount of bleeding at the site of injection and in patients, infected with blood-born diseases, this could increase the transmission of such disease to the partner.

DOSAGE AND DIRECTIONS FOR USE:

Alprostadil is administered by direct intracavernosal injection. A 27 - 30 gauge needle is recommended.

The first injection 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. The intracavernosal injection must be done under clean conditions and the vial and injection site must be cleaned with the swabs provided. The site of injection is usually along the dorso-lateral aspect of the proximal third of the penis. Visible veins should be avoided.

The side of the penis that is injected and the site of the injection must be alternated.

The injection site must be compressed (using an alcohol swab to cover the injection site) until the bleeding has stopped.

The dose of CAVERJECT should be individualised for each patient by careful titration under supervision by a physician. 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 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 10 to 20 micrograms. Doses greater than 60 micrograms of alprostadil are not recommended. While on self-injection, it is recommended that the patient visits the prescribing physician’s office every 3 months. At that time, the efficacy and safety of the therapy should be assessed and the dose of CAVERJECT should be adjusted if needed.

Reconstitution of injection:

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 pre-filled 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 27 gauge needle. Adjust volume to the required dose for injection. Following administration, any unused contents of the vial or syringe should be discarded.

As an aid to aetiologic diagnosis:

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 (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT) should be employed to prevent a risk of priapism prior to the

subject leaving the clinic. Over 80 % of subjects may be expected to respond to a single 20 microgram 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.

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 (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT) should be employed to prevent a risk of priapism prior to the subject leaving the clinic. At the time of discharge from the clinic, the erection should have subsided entirely and the penis must be in a completely flaccid state.

Treatment:

Erectile dysfunction of vasculogenic, psychogenic or mixed aetiology:

The initial dose of alprostadil 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. The patient must stay in the physician's office until complete detumescence occurs. If there is a response, then there should be at least a 1-day interval before the next dose is given.

Erectile dysfunction of pure neurogenic (spinal cord injury) aetiology:

Dose titration should be initiated at 1,25 micrograms. 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 60 minutes. If there is no response to the administered dose, then the next higher dose may be given within 1 hour. The patient must stay in the physician's office until complete detumescence occurs. If there is a response, then 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.

Reconstitution and storage:

Only the supplied diluent should be used to prepare solutions.

Reconstituted solutions are physically and chemically stable for a period of 24 hours at room temperature and for 7 days in the fridge if stored in the original container. Do not store the unused pack or reconstituted solution in a freezer.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

The most frequent adverse reaction after intracavernosal injection of CAVERJECT is penile pain. In studies, 34 % 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.

Painful erection is more likely to occur in patients with anatomical deformities of the penis, such as angulation, phimosis, cavernosal fibrosis, Peyronie's disease or plaques.

Haematoma at the site of injection, which is related to the injection technique rather than to the effects of alprostadil, occurs less frequently (3 %).

In a small number of patients prolonged erection (defined as an erection which lasts 4 – 6 hours) and/or priapism (defined as an erection which lasts 6 hours or longer) may occur. In the majority of cases, spontaneous detumescence occurred.

The following local adverse reactions occurred in a small number of patients: injection site ecchymosis, penile rash, penile oedema, and penile fibrosis. The following local adverse reactions were reported by fewer than 1 % of patients: balanitis, injection site haemorrhage, injection site inflammation, injection site itching, injection site swelling, urethral bleeding, and penile warmth, numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, erythema, venous leak, painful erection, and abnormal ejaculation.

In terms of systemic events, the following were reported for fewer than 1 % of patients in clinical studies, and were judged to be possibly related to CAVERJECT use: testicular pain, testicular swelling, scrotal erythema, pain or tightness, urinary frequency, urinary urgency, impaired urination, hypotension, vasodilatation, hypertension, supraventricular extrasystole, peripheral vascular disorder, dizziness, hypaesthesia, buttock weakness, localized pain (buttocks pain, leg pain, genital pain, abdominal pain), headache, pelvic pain, back pain, flu syndrome.

Haemodynamic changes, manifested as decreases in blood pressure and increases in pulse rate, were observed during clinical studies, principally at doses above 20 micrograms and above 30 micrograms of CAVERJECT, respectively, and appeared to be dose-dependent. However, these changes were usually clinically unimportant; only 3 patients (0,2 %) discontinued the treatment because of symptomatic hypotension.

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

Interactions: None known. Not intended for co-administration with any other agent for the treatment of erectile dysfunction.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 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.
Treatment should be according to established medical practice.
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. If still unsuccessful, intracavernosal 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 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.

IDENTIFICATION:

CAVERJECT 20 µg Powder for injection: A white to off-white lyophilised powder
BACTERIOSTATIC WATER FOR INJECTION: Clear, colourless liquid, free of particles.
The reconstituted product is a clear, colourless solution.

PRESENTATION:

The following components are included in the pack:
CAVERJECT 20 µg Powder for injection: A single dose vial containing a white to off-white lyophilised powder.
BACTERIOSTATIC WATER FOR INJECTION: A pre-filled syringe containing the diluent solution which is 1 ml Bacteriostatic Water for Injections and benzyl alcohol 0,9 % w/v; 2 syringe needles and 2 swabs.

STORAGE INSTRUCTIONS:

CAVERJECT must be stored at or below 25 °C. Reconstituted solutions are physically and chemically stable for a period of 24 hours at room temperature and 7 days under refrigeration if stored in the original container. Do not store the unused pack or reconstituted solution in a freezer.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

CAVERJECT 20 µg Powder for injection: 28/7.1/0329
BACTERIOSTATIC WATER FOR INJECTION: H/34/60

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

Pfizer Laboratories (Pty) Ltd
85 Bute Lane
Sandton 2196
South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT

16 October 2001

NAMIBIA: S2
Reg. No.: 04/7.1/0720

ZAMBIA: POM
Reg. No.: 198/010