

CAVERJECT **
P&U Proposed Physician Insert (clean) – 6-10-02

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3 **CAVERJECT® ****
4 alprostadil for injection

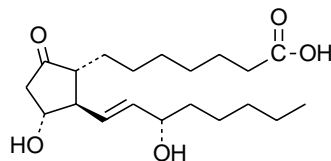
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6 **For Intracavernosal Use**

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8 **DESCRIPTION**

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10 CAVERJECT contains alprostadil as the naturally occurring form of prostaglandin E₁ (PGE₁) and is designated
11 chemically as (11 α ,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid. The molecular weight is 354.49.

12
13 Alprostadil is a white to off-white crystalline powder with a melting point between 115° and 116°C. Its solubility
14 at 35°C is 8000 micrograms (mcg) per 100 milliliter double distilled water.

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16 The structural formula of alprostadil is represented below:



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20 CAVERJECT ** is available as a disposable, single-dose, dual chamber syringe system. The system includes a
21 glass cartridge which contains sterile, freeze-dried alprostadil in the front chamber and sterile bacteriostatic
22 water for injection in the rear chamber. The alprostadil is reconstituted with the sterile bacteriostatic water just
23 before injection. CAVERJECT ** is available in two strengths for intracavernosal administration:

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25 **10 microgram** – The reconstituted solution has a volume of 0.64 mL. The delivered volume, 0.5 mL, contains
26 10 micrograms (mcg) of alprostadil, 324.7 mcg of alpha cyclodextrin, 45.4 mg of lactose, 23.5 mcg of sodium
27 citrate, and 4.45 mg of benzyl alcohol.

28
29 **20 microgram** – The reconstituted solution has a volume of 0.64 mL. The delivered volume, 0.5 mL, contains
30 20 micrograms (mcg) of alprostadil, 649.3 mcg of alpha cyclodextrin, 45.4 mg of lactose, 23.5 mcg of sodium
31 citrate, and 4.45 mg of benzyl alcohol.

32
33 When necessary, the pH of the alprostadil for injection was adjusted with hydrochloric acid and/or sodium
34 hydroxide before lyophilization.

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36 **CLINICAL PHARMACOLOGY**

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38 Alprostadil has a wide variety of pharmacological actions; vasodilation and inhibition of platelet aggregation are
39 among the most notable of these effects. In most animal species tested, alprostadil relaxed retractor penis and
40 corpus cavernosum urethrae *in vitro*. Alprostadil also relaxed isolated preparations of human corpus cavernosum
41 and spongiosum, as well as cavernous arterial segments contracted by either noradrenaline or PGF_{2 α} *in vitro*. In
42 pigtail monkeys (*Macaca nemestrina*), alprostadil increased cavernous arterial blood flow *in vivo*. The degree
43 and duration of cavernous smooth muscle relaxation in this animal model was dose-dependent.

CAVERJECT **
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45 Alprostadil induces erection by relaxation of trabecular smooth muscle and by dilation of cavernosal arteries.
46 This leads to expansion of lacunar spaces and entrapment of blood by compressing the venules against the tunica
47 albuginea, a process referred to as the corporal veno-occlusive mechanism.

48 49 **Pharmacokinetics**

50
51 **Absorption:** For the treatment of erectile dysfunction, alprostadil is administered by injection into the corpora
52 cavernosa. The absolute bioavailability of alprostadil has not been determined.

53
54 **Distribution:** Following intracavernosal injection of 20 mcg alprostadil, mean peripheral plasma concentrations
55 of alprostadil at 30 and 60 minutes after injection (89 and 102 picograms/mL, respectively) were not
56 significantly greater than baseline levels of endogenous alprostadil (96 picograms/mL). Plasma levels of
57 alprostadil were measured using a radioimmunoassay method. Alprostadil is bound in plasma primarily to
58 albumin (81% bound) and to a lesser extent I-globulin IV-4 fraction (55% bound). No significant binding to
59 erythrocytes or white blood cells was observed.

60
61 **Metabolism:** Alprostadil is rapidly converted to compounds which are further metabolized prior to excretion.
62 Following intravenous administration, approximately 80% of circulating alprostadil is metabolized in one pass
63 through the lungs, primarily by beta- and omega-oxidation. Hence, any alprostadil entering the systemic
64 circulation following intracavernosal injection is very rapidly metabolized. Following intracavernosal injection
65 of 20 mcg alprostadil, peripheral levels of the major circulating metabolite, 13,14-dihydro-15-oxo-PGE₁,
66 increased to reach a peak 30 minutes after injection and returned to pre-dose levels by 60 minutes after injection.

67
68 **Excretion:** The metabolites of alprostadil are excreted primarily by the kidney, with almost 90% of an
69 administered intravenous dose excreted in urine within 24 hours post-dose. The remainder of the dose is
70 excreted in the feces. There is no evidence of tissue retention of alprostadil or its metabolites following
71 intravenous administration.

72 73 **Pharmacokinetics in Special Populations**

74
75 **Geriatric:** The potential effect of age on the pharmacokinetics of alprostadil has not been formally evaluated. In
76 patients with acute respiratory distress syndrome (ARDS), the mean (\pm SD) pulmonary extraction of alprostadil
77 was 72% \pm 15% in 11 elderly patients aged 65 years or older (mean, 71 \pm 6 years) and 65% \pm 20% in 6 young
78 patients aged 35 years or younger (mean, 28 \pm 5 years).

79
80 **Pediatric:** Alprostadil plasma concentrations were measured in 10 neonates (gestational age of 34 weeks in 2
81 infants and 38 to 40 weeks in 8 infants) receiving steady-state intravenous infusions of alprostadil to treat
82 underlying cardiac malformations. Infusion rates of alprostadil ranged from 5 to 50 (median, 45)
83 nanograms/kilogram/minute, resulting in alprostadil plasma concentrations ranging between 22 and 530
84 (median, 56) picograms/mL. The wide range of alprostadil plasma concentrations in neonates reflects high
85 variability in individual clearances of alprostadil in this patient population.

86
87 **Gender:** The potential influence of gender on the pharmacokinetics of alprostadil has not been formally studied
88 in healthy subjects. Two studies determined the pulmonary extraction of alprostadil following intravascular
89 administration in 23 patients with ARDS. The mean (\pm SD) pulmonary extraction was 66% \pm 20% in 17 male
90 patients and 69% \pm 18% in 6 female patients, suggesting that the pharmacokinetics of alprostadil are not
91 influenced by gender.

92
93 **Race:** The potential influence of race in the pharmacokinetics of alprostadil has not been formally evaluated.

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95 **Renal and Hepatic Insufficiency:** The pharmacokinetics of alprostadil have not been formally studied in
96 patients with renal or hepatic insufficiency.

97
98 **Pulmonary Disease:** The pulmonary extraction of alprostadil following intravascular administration was
99 reduced by 15% ($66 \pm 3.2\%$ vs $78 \pm 2.4\%$) in patients with ARDS compared with a control group of patients
100 with normal respiratory function who were undergoing cardiopulmonary bypass surgery. Pulmonary clearance
101 was found to vary as a function of cardiac output and pulmonary intrinsic clearance in a group of 14 patients
102 with ARDS or at risk of developing ARDS following trauma or sepsis. In this study, the extraction efficiency of
103 alprostadil ranged from subnormal (11%) to normal (90%), with an overall mean of 67%.

104
105 **Drug-Drug Interactions:** The potential for pharmacokinetic drug-drug interactions between alprostadil and
106 other agents has not been formally studied.

107 108 **CLINICAL STUDIES**

109
110 The safety and efficacy of CAVERJECT Sterile Powder was investigated in men with a diagnosis of erectile
111 dysfunction due to psychogenic, vasculogenic, neurogenic, and/or mixed etiology in two well-controlled studies
112 (Study 1 and Study 2) and in one 6-month open-label study (Study 3).

113
114 Study 1: One hundred fifty-three men with a mean age of 53 years (range 23-69 years) were enrolled. The study
115 had three phases: a 2.5 week double-blind, in-office randomized crossover phase in which each man received
116 placebo or 2.5 mcg, 5 mcg, 7.5 mcg, or 10 mcg of CAVERJECT Sterile Powder; a 2 week open-label, in-office
117 dose-titration phase to identify the optimum home-use dose (the latter dose was defined as a dose inducing an
118 erection sufficient for penetration and lasting ≤ 60 minutes); and a 4-week open-label, self-injection phase. In
119 the double-blind phase, each dose of CAVERJECT was significantly more effective than placebo by clinical
120 evaluation (“full penile rigidity”) and by RigiScan criteria ($\geq 70\%$ rigidity for at least 10 minutes); there was no
121 response to placebo. The percentage of responders increased with increasing doses of CAVERJECT. The
122 overall response in the dose-ranging phases was 76% (117/153) by clinical evaluation and 51% (78/152) by
123 RigiScan criteria. The optimum dose for self-injection ranged from 1.25 to 65 mcg (median 20 mcg). Seventy-
124 three percent of the injections in 102 men who self-injected CAVERJECT resulted in satisfactory intercourse.
125 Seventy-five percent of the patients remained on the dose identified during the dose-ranging phase; 17% and 8%
126 of the patients slightly decreased or increased the dose, respectively. The mean duration of erection per
127 injection was 70.8 minutes.

128
129 Study 2: Two hundred ninety-six men with a mean age of 53.8 years (range 21-74 years) were enrolled in this
130 parallel-design, double-blind study. The men were randomly assigned to one of five groups and received either a
131 single dose of placebo, 2.5 mcg, 5 mcg, 10 mcg, or 20 mcg of CAVERJECT Sterile Powder. No patient
132 responded to placebo. The differences in the response rates in both the clinical and the RigiScan evaluations
133 between each of the doses of CAVERJECT and placebo were statistically significant. There was also a
134 statistically significant dose-response relationship with higher clinical response rates and higher RigiScan
135 response rates with increasing doses of CAVERJECT (with exception of the 10-mcg dose). The mean duration
136 of erection after injection ranged from 12 minutes after the 2.5-mcg dose to 44 minutes after the 20-mcg dose
137 and the relationship was linear ($p = .025$, linear regression analysis).

138
139 Study 3: The safety and efficacy of CAVERJECT Sterile Powder was evaluated in a 6-month, open-
140 label study in 683 men with a mean age of 58 years (range 20-79 years). The optimum dose of
141 CAVERJECT was established by titration in 89% of men (606/683). Four hundred seventy-one men
142 (69%) completed the 6-month study. At the start of the study, the mean dose was 17.7 mcg of
143 CAVERJECT and at the end of the study it was 20.7 mg. Eighty-seven percent of the 13,762

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144 injections of CAVERJECT, administered by self-injection by the men in the study, resulted in
145 satisfactory sexual activity. The mean duration of erection was 67.5 minutes.

146

147 The formulation of alprostadil contained in CAVERJECT ** includes the inactive excipient alpha cyclodextrin.
148 This formulation was compared with CAVERJECT Sterile Powder in 87 men in a single-blind, crossover study
149 designed to evaluate efficacy and safety. The doses used by the patients in the study ranged from 2.5 mcg to 20
150 mcg and were the same for both formulations. The efficacy of the two formulations was shown to be
151 comparable, as assessed by the 30-point erectile function (EF) domain score from the International Index of
152 Erectile Function (IIEF) and by a physician-assessment score for erectile response. The mean EF domain scores
153 for CAVERJECT Sterile Powder and the formulation contained in CAVERJECT ** were 26.6 (SD=5.3) and
154 27.6 (SD=3.8), respectively. The mean physician's assessment scores for CAVERJECT Sterile Powder and the
155 formulation contained in CAVERJECT ** were 2.6 (SD=0.6) and 2.7 (SD=0.5), respectively, based on a scale
156 of 0 (no tumescence) to 3 (full rigidity).

157

158 **INDICATION AND USAGE**

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160 CAVERJECT (CAVERJECT **, CAVERJECT Sterile Powder, and CAVERJECT Injection) is indicated for
161 the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

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163 Intracavernosal CAVERJECT is also indicated as an adjunct to other diagnostic tests in the diagnosis of erectile
164 dysfunction.

CAVERJECT **
P&U Proposed Physician Insert (clean) – 6-10-02

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CONTRAINDICATIONS

CAVERJECT should not be used in patients who have a known hypersensitivity to the drug, in patients who have conditions that might predispose them to priapism, such as sickle cell anemia or trait, multiple myeloma, or leukemia, 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 CAVERJECT.

CAVERJECT is intended for use in adult men only.

CAVERJECT is not indicated for use in children or newborns.

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

WARNINGS

Prolonged erection defined as erection lasting > 4 to ≤ 6 hours in duration occurred in 4% of 1,861 patients treated up to 18 months in studies of CAVERJECT Sterile Powder. The incidence of priapism (erections lasting > 6 hours in duration) was 0.4% with the same length of use. Pharmacologic intervention and/or aspiration of blood from the corpora cavernosum was performed in 2 of the 7 patients with priapism. To minimize the chances of prolonged erection or priapism, CAVERJECT should be titrated slowly to the lowest effective dose (see DOSAGE AND ADMINISTRATION). The patient must be instructed to immediately report to his prescribing physician, or, if unavailable, to seek immediate medical assistance for any erection that persists longer than 4 hours. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

PRECAUTIONS

General Precautions

1. CAVERJECT ** is designed for one use only. Following a single use, the injection device and any remaining solution should be properly discarded.
2. The overall incidence of penile fibrosis, including Peyronie's disease, reported in clinical studies with CAVERJECT Sterile Powder was 3%. In one self-injection clinical study where duration of use was up to 18 months, the incidence of fibrosis was 7.8%.

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.
3. Intracavernous injections of CAVERJECT can lead to increased peripheral blood levels of PGE₁ and its metabolites, especially in those patients with significant corpora cavernosa venous leakage. Increased peripheral blood levels of PGE₁ and its metabolites may lead to hypotension and/or dizziness.
4. Patients on anticoagulants, such as warfarin or heparin, may have increased propensity for bleeding after intracavernosal injection.
5. Underlying treatable medical causes of erectile dysfunction should be diagnosed and treated prior to initiation of therapy with CAVERJECT.

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P&U Proposed Physician Insert (clean) – 6-10-02

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6. The safety and efficacy of combinations of CAVERJECT and other vasoactive agents have not been systematically studied. Therefore, the use of such combinations is not recommended.
7. CAVERJECT ** uses a superfine (29 gauge) needle. As with all superfine needles, the possibility of needle breakage exists. Careful instruction in proper patient handling and injection techniques may minimize the potential for needle breakage.
8. The patient should be instructed not to re-use or to share needles or syringes. As with all prescription medicines, the patient should not allow anyone else to use his medicine.

Information for the Patient:

To ensure safe and effective use of CAVERJECT, the patient should be thoroughly instructed and trained in the self-injection technique before he begins intracavernosal treatment with CAVERJECT at home. The desirable dose should be established in the physician's office.

Any reconstituted solution with precipitates or discoloration should be discarded. The CAVERJECT ** syringe system is designed for one use only and should be discarded after use. The device and the needle must be properly discarded after use. Needles must not be re-used or shared with other persons. Patient instructions for administration are included in each package of CAVERJECT **.

The dose of CAVERJECT that is established in the physician's office should not be changed by the patient without consulting the physician. The patient may expect an erection to occur within 5 to 20 minutes. A standard treatment goal is to produce an erection lasting no longer than 1 hour. Generally, CAVERJECT should be used no more than 3 times per week, with at least 24 hours between each use.

Patients should be aware of possible side effects of therapy with CAVERJECT; the most frequently occurring is penile pain after injection, usually mild to moderate in severity. A potentially serious adverse reaction with intracavernosal therapy is priapism. Accordingly, the patient should be instructed to contact the physician's office immediately or, if unavailable, to seek immediate medical assistance if an erection persists for longer than 4 hours.

The patient should report any penile pain that was not present before or that increased in intensity, as well as the occurrence of nodules or hard tissue in the penis to his physician as soon as possible. As with any injection, an infection is a possibility. Patients should be instructed to report to the physician any penile redness, swelling, tenderness or curvature of the erect penis. The patient must visit the physician's office for regular checkups for assessment of the therapeutic benefit and safety of treatment with CAVERJECT.

Note: Use of intracavernosal CAVERJECT offers no protection from the transmission of sexually transmitted diseases. Individuals who use CAVERJECT should be counseled 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 (see ADVERSE REACTIONS section—hematoma, ecchymosis, hemorrhage at the site of injection). In patients infected with blood-borne diseases, this could increase the risk of transmission of blood-borne diseases between partners.

CAVERJECT **
P&U Proposed Physician Insert (clean) – 6-10-02

265 In clinical trials, concomitant use of agents such as antihypertensive drugs, diuretics, antidiabetic agents
266 (including insulin), or non-steroidal anti-inflammatory drugs had no effect on the efficacy or safety of
267 CAVERJECT.

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269 **Carcinogenesis, Mutagenesis, and Impairment of Fertility:**

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271 Long-term carcinogenicity studies have not been conducted. Rat reproductive studies indicate that alprostadil at
272 doses of up to 0.2 mg/kg/day does not adversely affect or alter rat spermatogenesis, providing a 200-fold margin
273 of safety compared with the usual human doses. The following battery of mutagenicity assays revealed no
274 potential for mutagenesis: bacterial mutation (Ames), alkaline elution, rat micronucleus, sister chromatid
275 exchange, CHO/HGPRT mammalian cell forward gene mutation, and unscheduled DNA synthesis (UDS).

276

277 A 1-year irritancy study was conducted in three groups of 5 male Cynomolgus monkeys injected
278 intracavernosally twice weekly with either vehicle or 3 or 8.25 mcg of alprostadil/ injection. An additional two
279 groups of 6 monkeys each were injected with vehicle or with 8.25 mcg/injection twice weekly as described
280 previously plus they received multiple doses during weeks 44, 48, and 52. Three monkeys from each group were
281 retained for a 4-week recovery period. There was no evidence of drug-related penile irritancy or nonpenile tissue
282 lesions, which could be directly related to alprostadil. The irritancy which was noted for control and treated
283 monkeys was considered to be a result of the injection procedure itself, and any lesions noted were shown to be
284 reversible. At the end of the 4-week recovery period, the histological changes in the penis had regressed.

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286 **Pregnancy, Nursing Mothers, and Pediatric Use:**

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288 CAVERJECT is not indicated for use in pediatric patients or women.

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P&U Proposed Physician Insert (clean) – 6-10-02

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ADVERSE REACTIONS

Local Adverse Reactions: The following local adverse reaction information was derived from controlled and uncontrolled studies of CAVERJECT Sterile Powder, including an uncontrolled 18-month safety study.

Local Adverse Reactions Reported by $\geq 1\%$ of Patients Treated with CAVERJECT Sterile Powder for up to 18 Months*

Event	CAVERJECT N = 1861
Penile pain	37%
Prolonged erection	4%
Penile fibrosis**	3%
Injection site hematoma	3%
Penis disorder***	3%
Injection site ecchymosis	2%
Penile rash	1%
Penile edema	1%

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* Except for penile pain (2%), no significant local adverse reactions were reported by 294 patients who received 1 to 3 injections of placebo.

** See General Precautions.

*** Includes numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, erythema, venous leak, penile skin tear, strange feeling of penis, discoloration of penile head, itch at tip of penis.

Penile Pain: Penile pain after intracavernosal administration of CAVERJECT was reported at least once by 37% of patients in clinical studies of up to 18 months in duration. In the majority of the cases, penile pain was rated mild or moderate in intensity. Three percent of patients discontinued treatment because of penile pain. The frequency of penile pain was 2% in 294 patients who received 1 to 3 injections of placebo.

Prolonged Erection/Priapism: In clinical trials, prolonged erection was defined as an erection that lasted for 4 to 6 hours; priapism was defined as erection that lasted 6 hours or longer. The frequency of prolonged erection after intracavernosal administration of CAVERJECT was 4%, while the frequency of priapism was 0.4% (see WARNINGS).

Hematoma/Ecchymosis: The frequency of hematoma and ecchymosis was 3% and 2%, respectively. In most cases, hematoma/ecchymosis was judged to be a complication of a faulty injection technique. Accordingly, proper instruction of the patient in self-injection is of importance to minimize the potential of hematoma/ecchymosis (see DOSAGE AND ADMINISTRATION).

The following local adverse reactions were reported by fewer than 1% of patients after injection of CAVERJECT: balanitis, injection site hemorrhage, injection site inflammation, injection site itching, injection site swelling, injection site edema, urethral bleeding, penile warmth, numbness, yeast infection, irritation, sensitivity, phimosis, pruritus, erythema, venous leak, painful erection, and abnormal ejaculation.

Systemic Adverse Events: The following systemic adverse event information was derived from controlled and uncontrolled studies of CAVERJECT Sterile Powder, including an uncontrolled 18-month safety study.

CAVERJECT **
P&U Proposed Physician Insert (clean) – 6-10-02

**Systemic Adverse Events Reported by \geq 1% of Patients Treated with CAVERJECT
Sterile Powder for up to 18 Months***

Body System/Reaction	CAVERJECT N = 1861
Cardiovascular System	
Hypertension	2%
Central Nervous System	
Headache	2%
Dizziness	1%
Musculoskeletal System	
Back pain	1%
Respiratory System	
Upper respiratory infection	4%
Flu syndrome	2%
Sinusitis	2%
Nasal congestion	1%
Cough	1%
Urogenital System	
Prostatic Disorder**	2%
Miscellaneous	
Localized pain***	2%
Trauma****	2%

- 325
326 * No significant adverse events were reported by 294 patients who received 1 to 3 injections of placebo.
327 ** prostatitis, pain, hypertrophy, enlargement
328 *** pain in various anatomical structures other than injection site
329 **** injuries, fractures, abrasions, lacerations, dislocations
330

331 The following systemic events, which were reported for < 1% of patients in clinical studies, were judged by
332 investigators to be possibly related to use of CAVERJECT: testicular pain, scrotal disorder, scrotal edema,
333 hematuria, testicular disorder, impaired urination, urinary frequency, urinary urgency, pelvic pain, hypotension,
334 vasodilation, peripheral vascular disorder, supraventricular extrasystoles, vasovagal reactions, hypesthesia,
335 non-generalized weakness, diaphoresis, rash, non-application site pruritus, skin neoplasm, nausea, dry mouth,
336 increased serum creatinine, leg cramps, and mydriasis.
337

338 Hemodynamic changes, manifested as decreases in blood pressure and increases in pulse rate, were observed
339 during clinical studies, principally at doses above 20 mcg and above 30 mcg of alprostadil, respectively, and
340 appeared to be dose-dependent. However, these changes were usually clinically unimportant; only three patients
341 discontinued the treatment because of symptomatic hypotension.
342

343 CAVERJECT had no clinically important effect on serum or urine laboratory tests.
344

345 The safety of CAVERJECT ** was evaluated in a study that compared the formulation of alprostadil for
346 injection contained in CAVERJECT ** with the formulation contained in CAVERJECT Sterile Powder. The
347 doses used by the 87 patients in this crossover study were the same for both formulations. The number and type
348 of events reported for CAVERJECT ** were consistent between formulations in this study and in other
349 controlled and uncontrolled studies with CAVERJECT Sterile Powder.
350

351 **OVERDOSAGE**
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P&U Proposed Physician Insert (clean) – 6-10-02

353 Overdosage was not observed in clinical trials with CAVERJECT. If intracavernous overdose of CAVERJECT
354 occurs, the patient should be under medical supervision until any systemic effects have resolved and/or until
355 penile detumescence has occurred. Symptomatic treatment of any systemic symptoms would be appropriate.
356

357 **DOSAGE AND ADMINISTRATION**

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359 The dose of CAVERJECT should be individualized for each patient by careful titration under supervision by the
360 physician. In clinical studies, patients were treated with CAVERJECT Sterile Powder in doses ranging from 0.2
361 to 140 mcg; however, since 99% of patients received doses of 60 mcg or less, doses of greater than 60 mcg are
362 not recommended. In general, the lowest possible effective dose should always be employed. In clinical studies,
363 over 80% of patients experienced an erection sufficient for sexual intercourse after intracavernosal injection of
364 CAVERJECT.
365

366 **Initial Titration in Physician's Office:**

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368 *Erectile Dysfunction of Vasculogenic, Psychogenic, or Mixed Etiology.* Dosage titration should be initiated at
369 2.5 mcg of alprostadil. The 10 mcg strength of CAVERJECT ** is designed to allow delivery of a 2.5 mcg dose
370 of alprostadil (see General Procedure for Solution Preparation). If there is a partial response at 2.5 mcg, the dose
371 may be increased by 2.5 mcg to a dose of 5 mcg within 1 hour. No more than 2 doses during initial titration
372 should be given within a 24-hour period. If additional titration is required, doses in increments of 5 to 10 mcg
373 may be given at least 24 hours apart until the dose that produces an erection suitable for intercourse and not
374 exceeding a duration of 1 hour is reached. If there is no response to the initial 2.5-mcg dose, the second dose
375 may be increased to 7.5 mcg within 1 hour. No more than 2 doses during initial titration should be given within
376 a 24-hour period. If additional titration is required, doses in increments of 5 to 10 mcg may be given at least 24
377 hours apart. The patient must stay in the physician's office until complete detumescence occurs.

378 *Erectile Dysfunction of Pure Neurogenic Etiology (Spinal Cord Injury).* Dosage titration should be initiated at
379 1.25 mcg of alprostadil. Because CAVERJECT ** is designed to deliver doses of 2.5 mcg or greater (see
380 General Procedure for Solution Preparation), CAVERJECT Sterile Powder or CAVERJECT Injection may be
381 used for an initial dose of 1.25 mcg. The initial dose may be increased by 1.25 mcg to a dose of 2.5 mcg within
382 1 hour. No more than 2 doses during initial titration should be given within a 24-hour period. If additional
383 titration is required, a dose of 5 mcg may be given during the next 24 hours. Thereafter, doses in increments of 5
384 mcg may be given at least 24 hours apart until the dose that produces an erection suitable for intercourse and
385 not exceeding a duration of 1 hour is reached. The patient must stay in the physician's office until complete
386 detumescence occurs.
387

388 The majority of patients (56%) in one clinical study involving 579 patients with erectile dysfunction of various
389 etiologies were titrated to doses of greater than 5 mcg but less than or equal to 20 mcg. The mean dose at the
390 end of the titration phase was 17.8 mcg of alprostadil.
391

392 **Maintenance Therapy:**

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394 The first injections of CAVERJECT must be done at the physician's office by medically trained personnel.
395 Self-injection therapy by the patient should be started only after the patient is properly instructed and well
396 trained in the self-injection technique. The physician should make a careful assessment of the patient's skills and
397 competence with this procedure. The intracavernosal injection must be done under sterile conditions. The site of
398 injection is usually along the dorso-lateral aspect of the proximal third of the penis. Visible veins should be
399 avoided. The side of the penis that is injected and the site of injection must be alternated; the injection site must
400 be cleansed with an alcohol swab.
401

402 The dose of CAVERJECT that is selected for self-injection treatment should provide the patient with an erection
403 that is satisfactory for sexual intercourse and that is maintained for no longer than 1 hour. If the duration of

CAVERJECT **
P&U Proposed Physician Insert (clean) – 6-10-02

404 erection is longer than 1 hour, the dose of CAVERJECT should be reduced. Self-injection therapy for use at
405 home should be initiated at the dose that was determined in the physician's office; however, dose adjustment, if
406 required (up to 57% of patients in one clinical study), should be made only after consultation with the physician.
407 The dose should be adjusted in accordance with the titration guidelines described above. The effectiveness of
408 CAVERJECT for long-term use of up to 6 months has been documented in an uncontrolled, self-injection study.
409 The mean dose of CAVERJECT Sterile Powder at the end of 6 months was 20.7 mcg in this study.
410 CAVERJECT ** in the 10 mcg strength is designed to deliver a minimum dose of 2.5 mcg and a maximum dose
411 of 10 mcg. CAVERJECT ** in the 20 mcg strength is designed to deliver a minimum dose of 5 mcg and a
412 maximum dose of 20 mcg. The physician should determine the most suitable formulation of CAVERJECT for
413 the individual patient (CAVERJECT **, CAVERJECT Sterile Powder, or CAVERJECT Injection).
414

415 Careful and continuous follow-up of the patient while in the self-injection program must be exercised. This is
416 especially true for the initial self-injections, since adjustments in the dose of CAVERJECT may be needed. The
417 recommended frequency of injection is no more than 3 times weekly, with at least 24 hours between each dose.
418 All formulations of CAVERJECT are intended for single use only and should be discarded after use. The user
419 should be instructed in the proper disposal of the injection materials (eg, device, needles).
420

421 While on self-injection treatment, it is recommended that the patient visit the prescribing physician's office every
422 3 months. At that time, the efficacy and safety of the therapy should be assessed, and the dose of CAVERJECT
423 should be adjusted, if needed.
424

425 **CAVERJECT as an Adjunct to the Diagnosis of Erectile Dysfunction:**

426
427 In the simplest diagnostic test for erectile dysfunction (pharmacologic testing), patients are monitored for the
428 occurrence of an erection after an intracavernosal injection of CAVERJECT. Extensions of this testing are the
429 use of CAVERJECT as an adjunct to laboratory investigations, such as duplex or Doppler imaging, ¹³³Xenon
430 washout tests, radioisotope penogram, and penile arteriography, to allow visualization and assessment of penile
431 vasculature. For any of these tests, a single dose of CAVERJECT that induces an erection with firm rigidity
432 should be used.
433

434 **General Procedure for Solution Preparation:**

435
436 CAVERJECT ** consists of a disposable, single-dose, dual-chamber syringe system. The system includes a
437 glass cartridge which contains sterile, freeze-dried alprostadil in the front chamber and sterile bacteriostatic
438 water for injection in the rear chamber. Following proper reconstitution instructions, the 10 mcg strength syringe
439 can deliver up to 0.5 mL of solution. Each 0.5 mL of solution contains 10 mcg of alprostadil, 324.7 mcg of
440 alpha cyclodextrin, 45.4 mg of lactose, 23.5 mcg of sodium citrate, and 4.45 mg of benzyl alcohol. The delivery
441 device can be set to deliver a solution volume of 0.125, 0.25, 0.375, or 0.50 mL to enable administration of 2.5,
442 5, 7.5, or 10 mcg of alprostadil. Following proper reconstitution instructions, the 20 mcg strength syringe can
443 deliver up to 0.5 mL of solution. Each 0.5 mL of solution contains 20 mcg of alprostadil, 649.3 mcg of alpha
444 cyclodextrin, 45.4 mg of lactose, 23.5 mcg of sodium citrate, and 4.45 mg of benzyl alcohol. The delivery
445 device can be set to deliver a solution volume of 0.125, 0.25, 0.375, or 0.50 mL to enable administration of 5,
446 10, 15, or 20 mcg of alprostadil. After reconstitution, the solution of CAVERJECT should be used within 24
447 hours when stored at or below 25°C (77°F). Parenteral drug products should be inspected visually for particulate
448 matter and discoloration prior to administration whenever the solution and container permit. The product should
449 not be used if particulate matter or discoloration are present. Following a single use, the injection device and any
450 remaining solution should be properly discarded.
451

452 **Caution: CAVERJECT ** is for single use only.** Do not use any remaining CAVERJECT solution.
453

454 **HOW SUPPLIED**

CAVERJECT **
P&U Proposed Physician Insert (clean) – 6-10-02

455

456 CAVERJECT ** is supplied as a disposable, single-dose, dual chamber syringe system. The system includes a
457 glass cartridge which contains sterile, freeze dried alprostadil in the front chamber and sterile bacteriostatic
458 water for reconstitution in the rear chamber. The syringes contain either 12.8 or 25.6 mcg of alprostadil to allow
459 delivery of a maximum of 10 or 20 mcg/0.5mL. Store the unreconstituted product at 25°C (77°F); excursions
460 permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
461

462 When reconstituted and used as directed, the deliverable amount for the 10 mcg strength is
463 10 mcg/0.5 mL or an increment of 10 mcg/0.5 mL, 2.5 mcg/0.125 mL, 5.0 mcg/0.25 mL, or 7.5 mcg/0.375 mL
464 of alprostadil and the deliverable amount for the 20 microgram strength is 20 mcg/0.5 mL or an increment of 20
465 mcg/0.5 mL, 5 mcg/0.125 mL, 10 mcg/0.250 mL, or 15 mcg/0.375 mL of alprostadil. The reconstituted solution
466 should be used within 24 hours when stored at or below 25°C (77°F).
467

468 CAVERJECT ** is supplied in a carton containing 2 blister trays. Each blister tray contains one dual chamber
469 syringe system, one needle and 2 alcohol swabs. It is available in the following strengths:

470 10 mcg NDC 0009-5181-01

471 20 mcg NDC 0009-5182-01

472

473 CAVERJECT is also available as follows:

474

475 CAVERJECT Sterile Powder (alprostadil for injection) packaged in vials, 6 vials per carton

476 • 10 mcg NDC 0009-3778-05

477 • 20 mcg NDC 0009-3701-05

478 • 40 mcg NDC 0009-7686-04

479

480 CAVERJECT Sterile Powder (alprostadil for injection) vials with diluent syringe, 6 syringe systems per carton

481 • 5 mcg NDC 0009-7212-03

482 • 10 mcg NDC 0009-3778-08

483 • 20 mcg NDC 0009-3701-01

484

485 CAVERJECT Injection ([alprostadil injection] aqueous), 5 ampoules per carton

486 • 10 mcg (10 mcg/mL) NDC 0009-7655-02

487 • 20 mcg (20 mcg/mL) NDC 0009-7654-02

488 • 40 mcg (40 mcg/2mL) NDC 0009-7650-02

489

490 **Rx only**

491

492 Manufactured for:

493 Pharmacia & Upjohn Company

494 A subsidiary of Pharmacia Corporation

495 Kalamazoo, MI 49001, USA

496

497 By:

498 Pharmacia AB

499 Stockholm, Sweden

500

501 Date (to be added)

502 Copy code (to be added)

[NOTE: the insert will contain a perforation to allow the Patient Instructions to be torn-off]

CAVERJECT **
P&U Proposed Physician Insert (clean) – 6-10-02

Patient Instructions For:

CAVERJECT® **
alprostadil for injection

Read this information carefully before using CAVERJECT [KAV-er-jeckt]. Read the information you get each time you renew your prescription, in case anything has changed. This is a summary and does not replace talking with your doctor when you start this medication and at check-ups. If you have any questions or concerns, talk to your doctor about them.

What is CAVERJECT?

CAVERJECT is a medicine to treat male impotence (erectile dysfunction). CAVERJECT is injected into a specific area of the penis and should produce an erection in 5 to 20 minutes. The erection should last for no longer than 1 hour.

CAVERJECT ** is for one use only and should be thrown away properly after a single use.

CAVERJECT does not protect you from sexually transmitted diseases (STDs), such as HIV (the virus that causes AIDS). In addition, small amounts of bleeding at the injection site can increase the risk of passing diseases carried by the blood, such as HIV.

What are the causes of and treatments for impotence?

There are several causes of impotence. These include medications that you may be taking for other conditions, poor blood circulation in the penis, nerve damage, emotional problems, too much smoking or alcohol use, use of street drugs, and hormonal problems. Often, impotence is due to more than one cause.

Treatments for impotence include switching medications if you are taking a medication that causes impotence, prescription medications, medical devices that produce an erection, surgical procedures to correct blood flow in the penis, penile implants, and psychological counseling.

You should not stop taking any prescription medications, unless told to do so by your doctor.

The use of other medical treatments for impotence in combination with CAVERJECT is not recommended. Discuss any concerns you may have about combination treatment with your doctor.

Who should not use CAVERJECT?

Do not use CAVERJECT if you have certain conditions that might cause long-lasting erections (lasting more than 4 hours). Long-lasting erections may cause penis damage. These conditions include:

- sickle cell anemia or trait
- leukemia
- tumor of the bone marrow (multiple myeloma)

Do not use CAVERJECT if you

- have a penile implant
- have an abnormally formed penis
- have other penis problems
- were told by your doctor not to have sex

Women and children should not use CAVERJECT.

How should I use CAVERJECT?

CAVERJECT **
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You will be treated with CAVERJECT in your doctor’s office to find out what dose is best for you. After that, you can inject it yourself at home. Do not use it more than 3 times a week. There should be at least 24 hours between doses. See your doctor for regular check-ups to be sure CAVERJECT is not causing damage and that it is working as well as possible.

See the section “Instructions for Use” at the end of this leaflet for details about how to use CAVERJECT.

What are the possible side effects of CAVERJECT?

About 4 in 100 men who use CAVERJECT may get erections that last more than 4 hours. These can cause serious and permanent damage. **Call your doctor or seek professional help immediately if you still have an erection 4 hours after injection.**

The most common side effect of CAVERJECT is mild to moderate pain after injection. About one-third of patients report this effect.

You may get a small amount of bleeding at the injection site. This is more likely if you have a medical condition or are taking a medicine that interferes with blood clotting.

Call your doctor if you notice any redness, lumps, swelling, tenderness, or curving of the erect penis. Also, tell your doctor about any penis pain you did not have before or other penis problems you have.

There is a possibility of needle breakage with use of CAVERJECT **. To best avoid breaking the needle, you should pay careful attention to your doctor’s instructions and try to handle the device properly. If the needle breaks during injection and you are able to see and grasp the broken end, you should remove it and contact your doctor. If you cannot see or cannot grasp the broken end, you should promptly contact your doctor.

How should I store CAVERJECT **?

1. Unmixed packages of CAVERJECT **, should be stored at room temperature. Temperatures between 59° to 86°F (15° to 30°C) are allowed. Avoid storing CAVERJECT ** at very high and very low temperatures.
2. During travel, do not let the medicine freeze or be stored at a temperature above 77°F (25°C). For example, do not store it in checked luggage during air travel or leave it in a closed automobile.
3. After mixing, CAVERJECT ** should be used within 24 hours. It should be kept at a temperature of 77°F or below during this storage time.

General advice about prescription medicines

Medicines are sometimes prescribed or purposes other than those listed in a Patient Information Leaflet. If you have any concerns about CAVERJECT, ask your doctor. Your doctor or pharmacist can give you information about CAVERJECT that was written for health care professionals. Do not use CAVERJECT for a condition for which it was not prescribed. Do not share CAVERJECT with other people.

You can get more information about impotence (erectile dysfunction) and its treatment from the National Institutes of Health (Washington, DC), the American Foundation for Urological Diseases (Baltimore, MD), or the Impotence Institute of America (Washington, DC).

.....
INSTRUCTIONS FOR USE

Before you use CAVERJECT, your doctor must train you in how to prepare and give the injection properly.

Before using CAVERJECT, talk to your doctor about what to expect when using it, possible side effects, and what to do if side effects occur. Your dose has been selected for your individual needs. Do not change your dose without consulting your doctor. If you are not sure of the volume or dose to be used, talk to your doctor or pharmacist.

CAVERJECT **
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Follow these instructions exactly to prepare and inject a sterile (germ-free) dose of CAVERJECT.

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Supplies Needed

CAVERJECT ** is packaged with a needle for injection (Figure A) and alcohol swab.

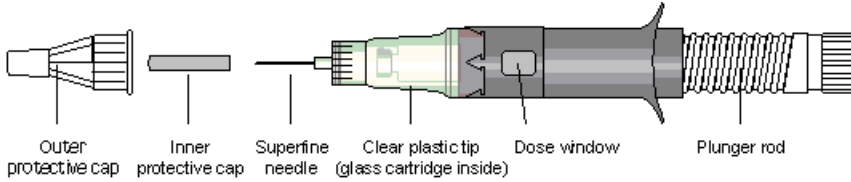


Figure A

CAVERJECT ** is available in 10 and 20 mcg strengths. **MAKE SURE YOU HAVE THE RIGHT STRENGTH OF CAVERJECT **.**

Prepare the Dose

1. Wash your hands thoroughly and dry them with a clean towel.
2. Remove the device, needle, and alcohol swabs from the blistered tray.
3. Using one of the alcohol swabs, clean the rubber membrane at the tip of the syringe (Figure B).

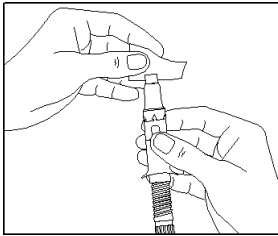


Figure B

4. Peel the paper lid from the needle (Figure C).

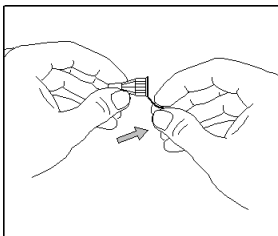


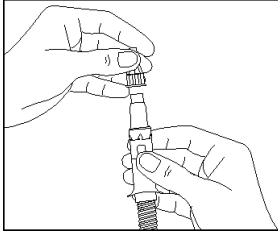
Figure C

CAVERJECT **

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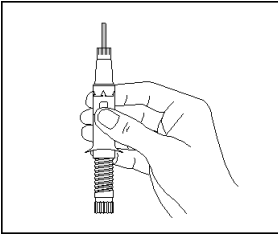
- Attach the needle to the device by pressing the needle on to the tip of the device and turning clockwise until the needle is firmly in place. Remove the outer protective cap from the needle (Figure D).

Figure D



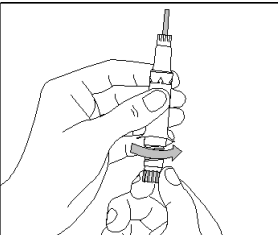
- Hold the device with the needle pointing upward. The white plunger rod is in the extended position (Figure E).

Figure E



- Turn the plunger rod slowly clockwise until it stops. This automatically mixes the alprostadil powder and the diluent. Turn the device upside down several times to make sure the solution is evenly mixed. The solution should be clear. Do not use it if it is cloudy or contains particles (Figure F).

Figure F

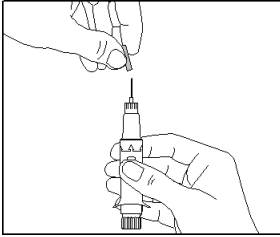


CAVERJECT **

P&U Proposed Physician Insert (clean) – 6-10-02

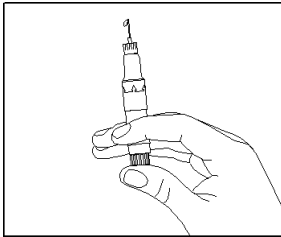
8. Hold the device with the needle upward and carefully remove the inner protective cap from the needle (Figure G).

Figure G



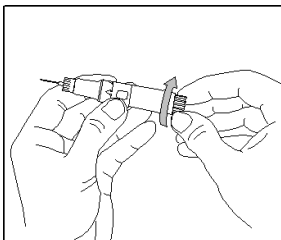
9. Keeping the device upright, press the plunger rod as far as it will go. A few drops will appear at the needle point and the solution will be free of bubbles although typically there may be some very small bubbles at the side of the glass cartridge (Figure H).

Figure H



10. Turn the end of the plunger rod clockwise slowly to choose the dose your physician has determined is appropriate for you. The number that appears in the window shows the dose in micrograms. If the number is higher than your prescribed dose, continue to turn the plunger rod clockwise slowly until you reach the correct dose (Figure I).

Figure I

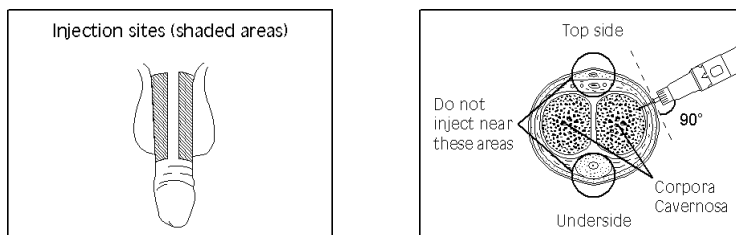


11. Set the device down on a level surface making sure the needle is not in contact with the surface.

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Select Injection Site

1. CAVERJECT ** will be injected into a corpus cavernosum (spongy tissue) of the penis. One corpus cavernosum runs the length of the right side of the penis. Another corpus cavernosum runs the length of the left side of the penis (see Figures J and K).



Figures J and K

2. Choose an injection site on one side of the shaft of the penis as shown in Figure J. **Avoid visible veins.**
3. **With each use of CAVERJECT, alternate the side of the penis and vary the site of injection.**

Inject Your Dose of CAVERJECT

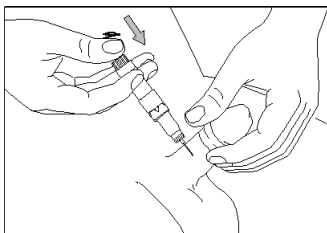
1. You should be sitting upright or slightly reclined when injecting CAVERJECT.
2. Holding the head of your penis with your thumb and forefinger, stretch your penis lengthwise along your thigh so that the skin is tight and you can clearly see the selected injection site.
3. Clean the injection site with a new alcohol swab. Do not discard this swab, you will need to use it again (see step 6).
4. Reposition the penis firmly against your thigh as in step 2 to keep it from moving during the injection.

CAVERJECT **

P&U Proposed Physician Insert (clean) – 6-10-02

5. Holding the device between your thumb and index finger, push the needle into the selected site through the skin and into the tissue as far as it will go. Push the plunger rod as far as it will go so the entire dose is injected (Figure L). If the injection solution does not flow easily, move the needle slightly and push as before. When using a dose less than the full capacity, a small amount of liquid will remain in the device.

Figure L



6. Grasp the device and pull the needle out of your penis. **Push on the injection site with the alcohol swab for about 5 minutes or until any bleeding stops.**
7. Carefully replace the outer protective cap on the needle.

Disposal of Injection Materials

After use, dispose of all injection materials safely. Your pharmacist may be able to supply a disposal box especially for disposable injection devices. **As with all prescription medicines, do not allow anyone else to use your medicine.**

Rx only

Manufactured for:
Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

By:
Pharmacia AB
Stockholm, Sweden

Date (to be added)
Copy code (to be added)

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this page is the manifestation of the electronic signature.**

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Daniel A. Shames
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