

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-212

MEDICAL REVIEW

NDA 21-212

SEP 28 2000

Date NDA submitted: January 20, 2000
Date NDA received: January 21, 2000
Draft review completed: September 12, 2000
Revisions completed: September 28, 2000

Medical Officer Review

Sponsor: Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

Drug: **Generic:** alprostadil for injection
Proposed Trade: CAVERJECT DC
Chemical: [11 α , 13E, 15S]-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid.

Route: intracavernosal

Dosage form: injection

Strength: 10 and 20 micrograms

Proposed indication: treatment of erectile dysfunction

Related INDs/NDAs: _____ (P & U Co.); NDA #20-379 and NDA #20-755
(P & U Co.)

Related documents: *Major amendments received:* none
Minutes of meetings dated: October 1, 1998 (Guidance/Pre-supplemental NDA)

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Sig _____

Distribution: Arch NDA 21-212
HFD-580/Div File
HFD-580/SAllen/DShames/KDavis-Bruno/JSalemme
HFD-860/VJarugula/AParekh

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1. Executive summary

1.1 Recommendation

From a clinical perspective, this reviewer recommends **approval** of this new drug application.

The sponsor has provided adequate controlled clinical data to support the pharmacodynamic "equivalence" of CAVERJECT Sterile Powder and CAVERJECT/alpha-cyclodextrin. A limited comparison of safety between the two groups did not reveal any new safety concerns.

Formal review by the Center for Devices and Radiologic Health (CDRH) concluded that the new dual-chamber device is substantially equivalent to other marketed injectors and poses no new safety concerns.

In terms of risk management actions and patient education materials, the proposed package insert is similar to the previously approved CAVERJECT Sterile Powder insert, and is generally considered adequate. However, as recommended by CDRH, the package insert will be modified to more prominently warn patients NOT to re-use the injector after one administration.

No Phase 4 studies are requested by this reviewer and no marketing restrictions are deemed necessary.

2. Summary of clinical findings

2.1 Brief overview of the clinical program

CAVERJECT DC is a new formulation of CAVERJECT Sterile Powder in a new dual-chamber injection device. It is intended for the treatment of men with erectile dysfunction. It is self-injected by patients directly into the penile shaft (or "corpora cavernosum").

The active drug substance in CAVERJECT is a well-known vasodilator, alprostadil (Prostaglandin E1). CAVERJECT DC contains a new excipient, alpha-cyclodextrin, which has been added to the formulation in order to reduce the amount of lactose and thus, reduce the overall volume of the dry drug product. Alpha-cyclodextrin will also serve to improve the shelf-life stability of CAVERJECT. Alprostadil complexed with alpha-cyclodextrin is already marketed for the treatment of ED as the product EDEX (Schwarz Pharma).

Based on a smaller volume of dry drug product and a longer shelf-life, the sponsor devised a dual-chamber syringe which would allow patients the convenience of simplified mixing of dry drug substance and diluent immediately prior to self-injection.

The sponsor and Division agreed that a standard bioequivalence study for this new formulation of CAVERJECT would not provide the necessary information to assure "bioequivalence".

Therefore, the sponsor submitted the results of a single controlled clinical trial in 87 patients (98-DUAL-001) which compared the pharmacodynamic effect and safety of the new formulation and previously approved CAVERJECT Sterile Powder.

In addition to the results of this single trial, the sponsor submitted references from the literature, disclosable information from FDA current documents, and a toxicological summary to support the safety of the excipient, alpha-cyclodextrin.

2.2 Efficacy:

In support of the pharmacodynamic equivalence of alprostadil sterile powder and alprostadil/alpha-cyclodextrin, the sponsor submitted the results from 98-DUAL-001.

In this study, 87 current users of CAVERJECT Sterile Powder were enrolled at 7 sites (six in the United States, and one in Germany). For purposes of comparison to the new formulation, patients completed a validated 4-week retrospective questionnaire (the 30-point erectile function [EF] domain from the International Index of Erectile Function [IIEF]) which quantitatively assessed their sexual experience in the previous month using CAVERJECT Sterile Powder. They also received a single in-office administration of CAVERJECT Sterile Powder including a physician-graded assessment of the erectile response.

After a brief washout period, patients returned for a single, in-office administration of CAVERJECT/alpha-cyclodextrin, followed by a 6-week at-home treatment period.

Therefore, this trial was designed as an open-label, crossover design, where the first-period, at-home results could be described as “retrospective” or “historical”.

The IIEF data and in-office assessments of erectile response clearly demonstrated that the two treatments were pharmacodynamically “equivalent” based on prior agreed-upon equivalence criteria.

The mean EF domain scores for CAVERJECT Sterile Powder and CAVERJECT/alpha-cyclodextrin were 26.6 (SD=5.3) and 27.6 (SD=3.8), respectively.

The mean physician’s assessment scores for CAVERJECT Sterile Powder and CAVERJECT/alpha-cyclodextrin were 2.6 (SD=0.6) and 2.7 (SD=0.5), respectively, based on a scale of 0 (no tumescence) to 3 (full rigidity).

Thus, these results clearly demonstrate equivalence and effectiveness. This reviewer believes that the trial design was adequate to meet the objectives of this particular trial.

2.3 Safety:

The reviewer agrees that there is adequate documentation from previous submissions (e.g. NDA 20-379) to support the safe use of alprostadil for this indication.

In terms of the **new formulation**, the sponsor submitted the following data to support safety:

1. The results from the single clinical trial 98-DUAL-001
2. Submitted literature references pertaining to the currently marketed alprostadil alfadex (EDEX), and
3. A toxicology summary specifically addressing the safety of alpha-cyclodextrin.

First, the safety results from 98-DUAL-001 revealed no new safety concerns in the CAVERJECT/alpha-cyclodextrin group compared to the currently approved CAVERJECT Sterile Powder group. However, the interpretation of these results is somewhat limited by several design issues, including: a historical (or “retrospective”) control group, a single treatment sequence, lack of blinding, relatively short duration of use (6 weeks), and relatively few patients (N=87).

The adverse reactions reported with the new formulation were similar in quality and quantity to the adverse reactions reported previously with CAVERJECT Sterile Powder. These included prolonged erection, penile pain, and injection site reaction. There were only two patients in whom erections were reported as being “prolonged” on the new formulation and yet not

prolonged on the old formulation. Neither of these events qualified as "priapism" and neither required intervention.

The submitted references from the literature pertaining to EDEX (alprostadil alfadex) actually provide good support for the safety of alprostadil alfadex.

Included in this submission were two abstracts and one full-length article. The two abstracts (1996 and 1997), authored by Goldstein et al for the Alprostadil Alfadex Study Group, revealed similar sorts of adverse reactions to CAVERJECT Sterile Powder, at reasonably similar frequencies. These include: penile pain (approximately 30-40%), prolonged erection (approximately 3-4%), and injection site reactions, such as bleeding (6-15%). In one of the abstracts, the rate of penile fibrotic nodules was reported as approximately 5%. These abstracts presented data from approximately 894 patients, for a total of almost 29,000 injections, over a 12-month period.

The full-length article by Porst, Buvat, Meuleman, Michal and Wagner (1998) described accumulated data from a 4-year, multicenter European trial in 162 patients who used EDEX. The extent of exposure included approximately 17,000 injections. The reported adverse reactions included penile pain (29% in the first year of use), penile injection site hematoma (33% in the first year of use), prolonged erections (N=2, or 1.2% in the first year of use), and finally, fibrotic changes (11.7% in the first year).

Fibrotic nodules occurred in 19 patients, at an average of 12 months from the initiation of injections, and after an average of 62 injections per patient. These nodules resolved in 9 patients following temporary discontinuation of therapy. In eight patients (4.9%), the nodules persisted. Fibrotic nodules are a known adverse event in a small percentage of patients following prolonged use of intracavernosal injections.

There were no untoward systemic reactions, including ECG and laboratory assessment.

Finally, the toxicology summary specifically addressing the safety of alpha-cyclodextrin, was indicative of an adequate safety margin. Alprostadil/alpha-cyclodextrin has been tested extensively in rats, dogs and monkeys. Studies have been performed via the intraperitoneal, intravenous and intraperitoneal approach.

There is no evidence of genotoxicity, carcinogenicity, or reproductive toxicity.

The target organ for toxicity for alpha-cyclodextrin is the kidney. Repeated subcutaneous dosing in rats revealed a NOAEL of ~~1000 mg/kg~~. Single doses of 1000 mg/kg elicited renal lesions consisting of ~~apical vacuolization~~ of the proximal convoluted tubules. These doses are far above the maximum recommended human dose of CAVERJECT/alpha-cyclodextrin, which will be 0.649 mg per injection or 0.013 mg/kg per injection.

Thus, based on the results of the single, controlled clinical trial, the reports from the literature, and a substantial amount of previous pre-clinical safety information, the reviewer believes that CAVERJECT/alpha-cyclodextrin has been demonstrated to be safe when administered as proposed.

3. Background:

3.1 Regulatory history: CAVERJECT Sterile Powder was approved for the treatment of erectile dysfunction on July 6, 1995. In order to improve patient convenience and ease-of-use, the sponsor developed a second CAVERJECT formulation, known as CAVERJECT Injection (alprostadil aqueous). This product was approved on November 30, 1997. CAVERJECT Injection is supplied as a frozen liquid, rather than a powder, and therefore does not require reconstitution. However, it must be kept frozen until the patient intends to use it, and then it must be slowly thawed.

Pharmacia has continued to pursue formulation changes to CAVERJECT in the hope of improving ease of use. On October 1, 1998, Pharmacia met with the Division to discuss a new formulation of CAVERJECT to be delivered in a new dual-chamber injection device. The new formulation would contain alpha-cyclodextrin, an excipient used to improve stability and reduce dry volume. By adding alpha-cyclodextrin, the sponsor would be able to reduce the amount of lactose and fit the dry drug substance in the front chamber of the new dual-chamber syringe. Alprostadil alphadex (containing alpha-cyclodextrin) is already approved for the treatment of ED as the drug product EDEX (Schwarz Pharma).

At the October 1, 1998 meeting, the sponsor stated their intention not to pursue any additional clinical testing for the new formulation. However, at the time, the sponsor was informed that a major formulation change would require a bioequivalence study. The sponsor and Division agreed that a typical bioequivalence study was not feasible in this circumstance due to rapid metabolism of alprostadil in the penile tissues, rapid, first-pass clearance in the lungs, and lack of measurable or meaningful plasma levels.

Therefore, the Division agreed to a "modified" bioequivalence study based on the pharmacodynamic endpoint of success in obtaining an erection sufficient for intercourse. In addition, a rough comparison of the safety of the two formulations would be conducted. The sponsor submitted a draft protocol for this Study, 98-DUAL-001, on December 7, 1999. The Division agreed with the basis of the draft. The sponsor submitted the final protocol on April 26, 1999 and the study was initiated on May 3, 1999.

It is important to note that the Division and sponsor agreed that the final study report for 98-DUAL-001 would serve as the major clinical support for the new formulation.

No Pre-NDA meeting was held with the sponsor.

3.2 Clinical background:

Erectile dysfunction has been defined as the consistent inability to attain and maintain an erection sufficient for sexual intercourse. The etiologies of this problem are numerous and include the following causes, just to name a few:

1. Vascular disorders such as atherosclerosis
2. Neurologic disorders such as diabetic neuropathy, multiple sclerosis, or spinal cord injury,
3. Metabolic and endocrine disorders such as hypogonadism
4. Psychologic disorders such as chronic depression
5. Iatrogenic disorders such as adverse events related to surgeries or concomitant medications.

Treatment for this problem has included the insertion of penile prosthesis, intracavernosal injection therapy, intraurethral insertion of vasoactive substances, and oral therapy (e.g. Viagra [sildenafil citrate]).

Treatment of the condition with self-injection of alprostadil directly into the corpora cavernosa is considered a safe, effective, and reliable means of attaining an erection sufficient for intercourse. However, there are clear drawbacks to such therapy. These include risk of prolonged erection, penile pain, development of penile fibrosis, patient fear, patient inconvenience, and difficulty in using the product.

In this application, the sponsor has endeavored to re-formulate the currently approved CAVERJECT Sterile Powder, in order to improve patient convenience and limit often cumbersome pre-injection preparation techniques.

3.3 Scientific rationale:

The self-injection of alprostadil into the intracavernous space is a well-recognized, effective and safe treatment for erectile dysfunction (ED). However, such treatment can require complicated reconstitution of solutions prior to use. Such procedures are often difficult for those patients with limited coordination and eyesight. In other patients, the procedure may be intimidating. Still others complain about the intrusion upon intimacy.

Therefore, in an effort to improve the self-delivery of alprostadil to the corpora, the sponsor intends to market their CAVERJECT product in a new delivery device, a dual-chamber syringe. Such a syringe could make use of CAVERJECT simpler and safer.

However, in order to market such a syringe, the sponsor found it necessary to alter the formulation of CAVERJECT in order to reduce its bulk. Thus, the sponsor made a major formulation change; specifically, alprostadil was complexed with alpha-cyclodextrin in order to create a drug product containing less lactose, less dry volume, and greater stability.

Thus, this application for CAVERJECT DC request marketing approval for a new formulation of CAVERJECT in a different injection device.

3.4 Clinical implications of the pre-clinical sections:

3.4.1 Chemistry, manufacturing and controls

In the CMC summary, the sponsor notes that the new formulation (alprostadil bound to alpha-cyclodextrin) will be more stable than the previous formulations, allowing for a longer shelf-life.

In his review of the new injection device, Von Nakayama of CDRH writes, "The CAVERJECT DC injection device does not raise any new questions of safety and effectiveness when used as intended and according to labeling. The device and functionality of the CAVERJECT DC injection device are substantially equivalent to legally marketed syringe devices." Dr. Nakayama goes on to comment that the sponsor should:

- a. Provide dose accuracy tests for the 2.5 microgram dose
- b. Include more prominent warnings/cautions against the re-use of the syringe.

Reviewer's comments:

1. The chemistry reviewer (Dr. Salemme) was asked to assess the in vitro data and decide on the need for additional dose accuracy tests for the 2.5 microgram dose.
2. The proposed physician and patient package inserts already contain statements warning against re-use of syringes. However, based on the recommendations of the CDRH reviewer, these statements will be made even more prominent.

3.4.2 Pharmacology/toxicology:

In this section, the sponsor comments that alpha-cyclodextrin is itself "considered to be a safe and well-documented excipient".

The sponsor notes that the maximum amount of alpha-cyclodextrin that can be delivered in a single dose is 0.65 mg, or approximately 11 micrograms/kilogram for an average 60 kilogram adult.

The sponsor comments that alpha-cyclodextrin complexed with alprostadil is currently used in the approved product EDEX, which is licensed by Schwarz Pharma for the intracavernosal injection in the treatment of ED. The sponsor notes that the "molar ratio of alprostadil to alpha-cyclodextrin in this formulation is the same as that in CAVERJECT DC". They note that the maximum alpha-cyclodextrin dose that may be delivered with EDEX is actually 1.3 mg (in a 40 mg dose of alprostadil), or twice the maximum proposed for CAVERJECT DC.

Non-clinical studies with CAVERJECT DC were not performed. The sponsor believes that the safety of the drug substance (alprostadil) is very well-known. In support of the safety of alprostadil/alpha-cyclodextrin and alpha-cyclodextrin alone, the sponsor submitted published scientific articles, disclosable approval information, and their own summary of the non-clinical toxicological documentation on alpha-cyclodextrin.

Reviewer's comment: The clinical reviewer and pharmacology reviewer agree that no new non-clinical studies are needed to support this application. For details, please refer to the Dr. Davis-Bruno's review. The clinical reviewer believes that the sponsor's arguments and documents support the safety of the excipient, alpha-cyclodextrin.

3.4.3 Human pharmacology included biopharmaceutics and metabolism:

The sponsor notes that complete information on the absorption, distribution, metabolism and excretion of alprostadil following intracavernosal administration have been previously submitted in NDA 20-379 (CAVERJECT Sterile Powder).

No additional studies to evaluate the pharmacokinetics of the new alprostadil/alpha-cyclodextrin formulation have been performed. The reason that such studies were not undertaken were because they were thought to be of limited value, for the following reasons:

1. Systemic levels of alprostadil are unlikely to reflect the pharmacodynamic effects in the corpora cavernosum
2. Prior studies characterizing systemic plasma concentrations and metabolites after intracavernosal administration have been submitted, and
3. The dissociation of alprostadil from the alprostadil/alpha-cyclodextrin complex is _____ and cyclodextrin would not be expected to result in differences in alprostadil disposition when compared to other formulations with identical amounts of alprostadil.

In support of #3, the sponsor submitted the results from a single, non-clinical study which determined the binding constant for the molecular complexation between alprostadil and alpha-cyclodextrin and used that value to estimate the percentage of alprostadil free upon injection of alprostadil/alpha-cyclodextrin.

In lieu of a standard bioequivalence study, the sponsor conducted Study 98-DUAL-001, a controlled clinical trial, that was designed in accord with the Division's recommendations. The results of this trial were submitted in this application.

3.5 Dose selection:

CAVERJECT Dual Chamber will be available in two strengths: 10 micrograms (mcg) of alprostadil and 20 mcg of alprostadil. Doses ranging from 2.5 mcg to 20 mcg were studied in the single, controlled clinical trial.

In the proposed patient instructions, the patient is instructed to use his own "individualized" dose, based on the results of an in-office, physician-supervised, dose-titration sequence.

The sponsor believes that the majority of patients will require doses in the range of 5 micrograms to 20 micrograms.

Reviewer's comment: CAVERJECT DC will be supplied in single-use syringes containing 10 mcg or 20 mcg. Therefore, patients requiring more than 20 micrograms will not be candidates for treatment with CAVERJECT DC. Such patients will have to use either CAVERJECT Sterile Powder or CAVERJECT Injection.

3.6 International marketing history:

CAVERJECT Sterile Powder is approved in 71 countries worldwide.

CAVERJECT Injection (alprostadil injection) aqueous is approved in 11 countries worldwide.

CAVERJECT Dual Chamber is not currently marketed anywhere in the world.

4. Contents of the clinical section of the NDA:

The clinical section of this NDA contained the following documents:

1. The final study report for the single, controlled clinical trial 98-DUAL-001.
2. The final study report for Study a0028158, entitled, "Determination by NMR of the binding constant for the molecular complex between alprostadil and alpha-cyclodextrin."
3. The clinical data summary from the original CAVERJECT Sterile Powder NDA (20-397).
4. The human pharmacokinetics and bioavailability summary from the original CAVERJECT Sterile Powder NDA (20-397).
5. Selected references from the literature, including one full-length published article and two published abstracts pertaining to alprostadil alphadex.

4.1 Materials assessed in the clinical review of the NDA:

This reviewer performed a clinical regulatory review of the following:

1. Study 98-DUAL-001 (see Appendix 1).
2. The published literature pertaining to alprostadil alphadex.
3. The sponsor's toxicology summary pertaining to alpha-cyclodextrin (from the Pharmacology section)

4.2 Safety update review:

On September 18, 2000, the sponsor submitted a clinical safety update. The report summarized all relevant safety data for CAVERJECT alpha-cyclodextrin from filing up to January 20, 2000. The sponsor also assessed their spontaneously reported adverse reaction database for CAVERJECT Sterile Powder and CAVERJECT Injection up to July 31, 2000.

Since the time of filing two additional clinical trials using CAVERJECT alpha-cyclodextrin have been conducted and are completed. The sponsor presented preliminary safety information from these two trials (139-URO-0089-0003 and 139-URO-0089-0004).

In the first trial, 63 males with ED received a single in-office dose of CAVERJECT alpha-cyclodextrin and CAVERJECT Sterile Powder in a crossover, blinded fashion. The dose of alprostadil ranged from 2.5 micrograms to 20 micrograms. Five patients experienced adverse events. One patient was discontinued after an adverse event (asthma after a 20 microgram dose of alprostadil alpha-cyclodextrin). This event was not believed to be treatment-related by the investigator. In only two patients, the adverse event was considered drug-related. One patient had mild pruritis after both formulations. One patient had mild penile pain after alprostadil alpha-cyclodextrin.

In the second trial, 22 males with ED received a single in-office dose of CAVERJECT alpha-cyclodextrin at the same dosage as their effective at-home dose. No adverse events were reported in this trial.

The data presented in this safety update provide no new safety concerns associated with CAVERJECT DC.

4.3 Review of package insert and labeling recommendations:

Clinical regulatory review of the package insert was performed. Six changes were recommended. Three of these involved more prominent statements against re-using the single-dose injector. Two changes pertained to clarifications of Study 98-DUAL-001 (in the Clinical Studies and Adverse Reactions sections). The last change was a recommendation to remove data pertaining to clinical trial results from the Dosage and Administration section.

These recommendations will be forwarded to the sponsor

Appendix A. Clinical trial 98-DUAL-001

A.1 Design and procedures: This was an open-label, crossover study conducted in 60 men with erectile dysfunction. The objective of this study was to demonstrate that two formulations of alprostadil (alprostadil sterile powder and alprostadil/ α -cyclodextrin) produced comparable pharmacodynamic effects when injected intracavernosally at the same dose levels. In lieu of standard "bioequivalence" testing, the real intent of this study was to provide evidence that the two compounds were "pharmacodynamically equivalent".

Reviewer's comment: It should be made clear that this clinical study was requested by the Division in order to demonstrate comparability of the two different formulations. In the face of an unusual route of administration (intracavernosal injection), minimal systemic absorption, and extremely rapid metabolism, the Division agreed that a standard "bioequivalence" study was not feasible. Instead, the Division believed that a "pharmacodynamic" demonstration of equivalence was appropriate.

The objective of this particular study, therefore, was to demonstrate pharmacodynamic equivalence of the two formulations, but NOT to assess the performance of the dual-chamber injector device. To this end, the reviewer believes that the device might actually have confounded the assessment of "bioequivalence". Therefore, the dual-chamber injector device was not included as part of this clinical trial.

This reviewer believes that the acceptable review by the Center for Devices (CDRH) regarding device-specific engineering and device-specific performance measures is adequate to support approval of the device, irrespective of the lack of actual clinical use data (see Consultation Review from Von Nakayama dated July 24, 2000).

In order to meet the study objective in the most efficient and convincing manner possible, it was agreed that the study population could be comprised of current, at-home users of a stable dose of alprostadil sterile powder for the treatment of erectile dysfunction (ED).

First-period data for this crossover trial was derived from this group's previous 4-week, at-home experience with a stable dose of alprostadil sterile powder. This experience was quantified using the International Index of Erectile Function (IIEF) questionnaire, a validated instrument for this purpose. In addition, a single dose of alprostadil sterile powder, at the patient's "usual" dose level, was administered in the clinic. The in-clinic erectile response was quantified by physician and patient assessments.

A washout period of 3-7 days followed the first period.

When patients returned for the second period of this crossover trial, they underwent another in-clinic, single-dose administration of alprostadil, this time using alprostadil/ α -cyclodextrin. The same dose of alprostadil was employed as in Period #1. The erectile response was again quantified by patient and physician assessments. Patients were then sent home with a sufficient supply of alprostadil/ α -cyclodextrin for 6 weeks. Erectile function and sexual activity experience for the last four weeks of Period 2 was then quantified using the IIEF questionnaire.

Reviewer's comments: This study included patients who had been using alprostadil sterile powder at doses from 2.5 micrograms up to 20 micrograms. The reason for excluding patients using more than 20 micrograms is that alprostadil/ α -cyclodextrin in the new dual-chamber syringe will be supplied in doses up to 20 micrograms only.

For purposes of comparison between the two periods, the primary efficacy endpoint was the 30-point, EF domain from the IIEF instrument. The primary objective of the study was to demonstrate "equivalence" between alprostadil sterile powder and alprostadil/ α -cyclodextrin.

The statistical analysis plan was designed to provide guidelines as to assess whether equivalence was demonstrated. In doing so, the sponsor proposed two "null hypotheses". These were:

1. The mean total score of the EF domain was at least 3 points higher for alprostadil sterile powder than for alprostadil/ α -cyclodextrin and
2. The mean total score was at least 3 points higher for alprostadil/ α -cyclodextrin than for alprostadil sterile powder.

In order to declare "equivalence" between the formulations, BOTH null hypotheses would have to be rejected. In order to reject both nulls, the 95% confidence intervals for the difference in mean total EF domain scores between the two groups would have to fit within the pre-defined equivalence limits of -3 to +3.

Secondary endpoints included other IIEF domain scores, the scores from the physician and patient assessments of rigidity following the in-office dose administrations, time to onset of erection and duration of erection.

Safety measurements included reported adverse events and vitals signs.

Reviewer's comment:

The study design included the following deficiencies:

1. **Laboratory measurements were not included as assessments of safety.**
2. **Direct assessments of penile pain were conducted only if the patient spontaneously reported pain.**

A.2 Disposition of patients and demographics:

The study was initiated on May 3, 1999 and completed on August 10, 1999. The study was conducted at 7 sites in the United States and 1 site in Germany. Although the protocol called for enrollment of 60 patients, a total of 87 patients were enrolled. Of these, 30 patients were enrolled at the single German site.

Only 4 patients withdrew from the trial. Of these, two patients withdrew due to adverse events. In one case, a patient was hospitalized for non-bacterial spinal meningitis and diabetic ketoacidosis approximately 5 weeks after his last dose of study medication. The other patient withdrew after experiencing mild-moderate penile pain after each of 4 injections of alprostadil/ α -cyclodextrin as well as moderate "dizziness" and moderate "body rashes" after the fourth dose.

The only protocol deviation of significance was that only two patients (2.3% of the study population) were enrolled who used 2.5 micrograms. The intent of the trial was to enroll at least 10% of the study population at the lowest dose.

At baseline, the mean patient age was 59 years with a range of 32 to 74 years. The majority of patients were Caucasian, with only 11 Black patients (12.6%). The mean duration of ED was approximately 79 months and the predominant etiology of ED was "arteriogenic" or "mixed". Approximately 16% were current smokers and 39% were former smokers. All 87 patients described at least one concomitant illness (e.g. hypertension in 39%) and 77% received at least one concomitant medication (most common being aspirin and multivitamins).

In regard to starting dosage, 37% of patients were taking the maximum allowed dose in this trial, 20 micrograms. Another 16% were taking 10 micrograms, 12% were taking 5 micrograms, and 10% were taking 15 micrograms. The remaining patients were taking various doses. Only 2.3% were taking the lowest dose, or 2.5 micrograms.

Reviewer's comment: Although only two patients were actually taking the lowest dose (2.5 micrograms), a total of five patients (or 5.7%) were taking doses less than 5 micrograms. This appears to be a reasonable assessment of formulation comparability at "low doses".

A.3 Efficacy analyses

Primary efficacy endpoint: As described above, the 30-point EF domain from the IIEF served as the primary efficacy endpoint in this trial. There were 83 of 87 patients (95.4%) with complete IIEF data for both periods. **The mean score for alprostadil sterile powder was 26.6 (SD=5.3). The mean score for alprostadil/ α -cyclodextrin was 27.6 (SD=3.8).**

Thus, the difference between these two means is 1.0. The 95% confidence interval for this difference is -0.1 to 2.2. This confidence interval is completely within the pre-defined equivalence limits (-3, 3). Thus, the sponsor concludes that both null hypotheses may be rejected and "equivalence" between the two formulations may be declared.

Reviewer's comment: The reviewer agrees that pharmacodynamic equivalence was demonstrated.

Table 13 of the final study report (Vol 16, page 98) demonstrates that the EF domain score for the alprostadil/ α -cyclodextrin period was equal to or better than the alprostadil sterile powder score for each dose level tested (2.5 micrograms to 20 micrograms).

It is important to note that the difference between treatments did not differ substantially between centers.

Secondary efficacy variables: As previously described, the patient's erectile response to a single, in-office administration was judged by the investigator and the patient, and scored on a 0 to 3 scale as follows: 0=no tumescence, 1=partial tumescence, 2=full tumescence, and 3=full rigidity.

There were 86 of 87 patients with data for both periods. The mean investigator's score for alprostadil sterile powder was 2.6 (SD=0.6). The mean investigator's score for alprostadil/ α -cyclodextrin was 2.7 (SD=0.5). The difference between these means was 0.1, with a confidence interval of -0.05 to 0.21. The mean patient's assessments were virtually identical to the investigator's assessments. Again, the mean scores for at each dose level were actually better for alprostadil/ α -cyclodextrin than for alprostadil sterile powder.

In terms of time to onset of erection, the mean onset was 9.0 minutes (SD=4.3) and 8.6 minutes (SD 3.9) for alprostadil sterile powder, and for alprostadil/ α -cyclodextrin, respectively. The mean difference was -0.3 minutes (SD=4.2) with 95% confidence limits of -1.2 and 0.6.

Finally, in terms of duration of erection, the mean duration was 61.6 minutes (SD=33.6) and 64.5 minutes (SD 30.2) for alprostadil sterile powder, and for alprostadil/ α -cyclodextrin, respectively. The mean difference was 2.9 minutes (SD=27.7) with 95% confidence limits of -3.1 and 8.8.

Reviewer's comment: The analysis of the secondary efficacy endpoints clearly supports the contention that the two formulations are pharmacodynamically equivalent.

A.4 Safety analyses

Extent of exposure: Eighty-seven patients enrolled in the trial. All of these patients received a single in-office dose of alprostadil sterile powder. Eighty-six patients received a single, in-office dose of alprostadil/ α -cyclodextrin. The actual doses administered ranged from 2.5 micrograms to 20 micrograms. Most patients were at 20 micrograms (37%), 10 micrograms (16%), 5 micrograms (11.5%) and 15 micrograms (10%).

In the at-home phase, all patients were distributed 12 injections. Sixty-seven patients, or 77%, used at least 8 injections. Another 15 patients (17%) used 5 to 7 injections. One patient used 4 injections. One patient was withdrawn prior to the at-home phase. Finally, 3 patients failed to return any used or unused injections but "according to the investigators, these patients had used the study medication during the home phase".

Deaths: There were no deaths reported in this study.

Serious adverse events: There was one serious adverse event reported.

Patient 111 was a 41 year old man with insulin-dependent diabetes mellitus, a history of drinking 5-6 bottles of beer per evening, and unspecified "polyneuropathy". On July 9, 1999, he was admitted to the hospital. He was disoriented, forgetful and somnolent. On physical examination, he had right-sided upper extremity weakness. His laboratory values revealed hyperglycemia and an elevated white blood cell count. Toxicology screen revealed qualitative evidence of benzodiazepines only.

Due to the presenting acute neurologic signs and symptoms, a lumbar puncture was performed revealing 240 polymorphonuclear leukocytes, without bacteria. CT scan of the brain did not reveal an infarct or a bleed. MRI of the brain, however, was described as revealing a right-sided lacunar infarct frontally versus a "fresh encephalitis focus". In addition, the MRI showed multiple areas of demyelination "peri- and paraventricular, especially including the corpus callosum" as well as non-specific, right-sided edema in the "temporo-occipito-parietal" region.

Presumptive diagnosis upon admission was diabetic ketoacidosis and bacterial meningitis. The patient was started on Rocephin, IV fluids and IV insulin. His disorientation quickly reversed. He then developed a skin allergic response to Rocephin requiring discontinuation of the antibiotic. Nevertheless, his recovery continued until his eventual discharge to a rehab facility on August 13, 1999.

Ultimately, cerebrospinal fluid cultures were determined to be negative for bacteria or "viruses".

On follow-up MRI of the brain did not reveal an infarct, there remained evidence of diffuse "microangiopathic brain parenchyma changes" consistent with diabetes mellitus. In addition, there remained evidence of multiple areas of periventricular demyelination, as well as "unchanged barrier disturbance" in the right "parieto-occipital" region.

Follow-up echocardiography was negative.

The final diagnoses listed in the hospital discharge summary were: diabetic ketoacidosis, alcohol withdrawal delirium, Koraskow syndrome, bacterial meningitis, cerebral microangiopathy, brain infarct, right occipital region.

The patient's last known injection of study medication was June 4, 1999, when he received a single dose of alprostadil/alpha-cyclodextrin. On that date, he was also distributed a six-week supply (12 injections) of alprostadil/alpha-cyclodextrin for the at-home period. On August 17, 1999, 4 days after hospital discharge, at the time of last contact between the investigator and this patient, the patient was unable to remember if he had used any injections between June 4, 1999 and the day of hospital admission, July 9, 1999. He informed the hospital staff that he had thrown all his remaining injections away. No injections were returned.

Reviewer's comment: In this case, it is not possible to determine a relationship between the patient's neurologic event and study medication.

Based on a negative CSF culture, the presumptive diagnosis of bacterial meningitis was not confirmed objectively.

It is unclear to this reviewer if the patient actually experienced a cerebrovascular infarct, although such an event appears most likely. Given the patient's 17-year history of insulin-dependent diabetes mellitus, and MRI revealing diffuse cerebral angiopathy, it is reasonable to assume that an infarct could represent progression of underlying vascular disease.

Ultimately, the reviewer believes that the relationship between this SAE and study medication is unknown but appears rather unlikely.

Discontinuation due to adverse events:

Patient 1005 withdrew after experiencing mild-moderate penile pain after each of 4 at-home injections of alprostadil/alpha-cyclodextrin, and moderate "dizziness" and moderate "body rashes" after the final dose. The events resolved without sequelae.

Patient 111 was described in the SAE section above.

Other significant adverse events:

Three patients reported prolonged erections, as follows:

Patient #1005 had a 2 hour 10 minute erection following his first in-office dose of alprostadil/alpha-cyclodextrin. His erection after the same dose of alprostadil sterile powder lasted 1 hour and 27 minutes. He ultimately discontinued after four at-home doses of 2.5 micrograms (lessened amount) due to penile pain.

Patient #1001 had a 2 hour 29 minute erection following his first dose of alprostadil/ α -cyclodextrin. His erection after the same dose of alprostadil sterile powder lasted 57 minutes. He did not report additional AEs in the at-home phase.

Finally, Patient #1007 had an erection of 3 hours and 20 minutes after an injection of alprostadil sterile powder (8 micrograms) at Visit 1. A reduced dose of alprostadil/ α -cyclodextrin (5 micrograms) at Visit 2 resulted in an erection lasting 1 hour and 30 minutes.

Reviewer's comment: Since there were two adverse events reported as "prolonged erection" on alprostadil/ α -cyclodextrin, the reviewer attempted to answer the question, "Does the new formulation induce more frequent prolonged erections?"

Does the new formulation induce more frequent prolonged erections?

Data regarding mean duration of erection was virtually identical between the two groups.

The reviewer performed an analysis which compared outliers for duration of erections (erection \geq 90 minutes, \geq 120 minutes, and \geq 180 minutes) between the two groups.

Table 1. Number of patients (% of total) who experienced an erection \geq 90 minutes.

Occurred after both injections	Occurred only after alprostadil/ α -CD	Occurred only after alprostadil St. Po.
N=7 (8.1%)	N=7 (8.1%)	N=6 (7.0%)

Table 2. Number of patients (% of total) who experienced an erection \geq 120 minutes.

Occurred after both injections	Occurred only after alprostadil/ α -CD	Occurred only after alprostadil St. Po.
N=4 (4.7%)	N=5 (5.8%)	N=1 (1.2%)

Only one patient experienced an erection of at least 180 minutes in duration (Patient #1007, only on alprostadil sterile powder).

In those patients in the second group (erection \geq 120 minutes) who had a longer duration on alprostadil/ α -CD, Table 3 depicts the per-patient differences.

Table 3. Individual patients who had a greater duration of erection on alprostadil/ α -CD and an erection of at least 120 minutes.

Patient #	Duration on Alprostadil/ α -CD	Duration on alprostadil St. Po.
#107	126 minutes	111 minutes
#806	121 minutes	32 minutes
#901	125 minutes	55 minutes
#1001	149 minutes	57 minutes
#1005	130 minutes	87 minutes

Reviewer's comment: Overall, the reviewer believes that this data does not reveal a clinically meaningful safety difference between the two groups in terms of inducing a longer duration (or "prolonged") erection.

In addition, the at-home experience did not reveal such a problem and further, there is no theoretic reason that the two formulations should be different in this regard.

Overall adverse events:

A total of 29 adverse events were reported by a total of 12 patients.

In the washout period

Two patients reported unrelated adverse events during the washout period (common cold and renal cyst).

Following in-clinic dosing

Three individual patients reported one adverse event each (prolonged erection) immediately following the single, in-clinic dosing. One patient reported the event after injection of alprostadil sterile powder, the others after injection of alprostadil/ α -cyclodextrin. These events were previously described under the heading "Other significant adverse events".

In the at-home period:

Four patients (4.6%) reported "penis disorder" (penile pain, post-injection pain, pain during erection, etc) in a total of 17 events. All of these events were described as mild, except one event described as moderate.

One patient reported hematospermia (1.1%). One patient reported hypercholesterolemia (1.1%).

One patient reported moderate dizziness (1.1%) and concomitant moderate "body rashes" (1.1%). (see "Discontinuations due to adverse events").

One patient reported "Combined diabetic ketoacidosis" and "bacterial meningitis" (see "Serious adverse events" section).

One patient (#124) reported "reddening of the injection site" and severe "temporary cardiac insufficiency".

Patient #124

Records indicate that Patient 124 was a 59 year old male with a history of diabetes mellitus, coronary atherosclerosis and "polyneuropathy". He was taking the following concomitant medications: insulin, molsidomine, and acetylsalicylic acid. He received in-office doses of both formulations. Both formulations resulted in "full tumescence" for approximately 40 minutes each.

According to drug accountability records, Patient 124 was dispensed 12 doses of alprostadil/ α -cyclodextrin at Visit 2 and returned all 12 doses used. According to efficacy data listings, his EF domain score for both periods was 29 (out of 30).

An adverse event of "reddening of injection site" is listed for this patient on page 203 of Volume 2. The event is described as "drug-related" and "mild" and occurring during the at-home period.

An additional adverse event is listed for the patient as "temporary cardiac insufficiency" ("cardiac failure"). The date of the event is listed as July 18, 1999. The investigator at the site reported that one hour after injection, the patient experienced difficulty breathing and "the feeling of having fluid in his lungs". The symptoms resolved completely without intervention. Two to three hours later, at bedtime, the patient experienced the same symptoms, which again resolved rapidly. He slept the night and the next day was without symptoms. He returned the next day for his final clinic visit. The investigator believed that the event was "not related".

Reviewer's comment: Based on the data available to this reviewer, it is not possible to determine definitively whether temporary cardiac insufficiency in Patient 124 was drug-related. However, given the patient's previous history of coronary arteriosclerosis and repeat episode of difficulty breathing 3 hours after injection, this event was probably not treatment-related.

Vital signs:

Supine blood pressure and heart rate were determined prior to dosing, then 15 and 60 minutes after each injection at the clinic.

Mean systolic and diastolic blood pressures at 15 and 60 minutes post-dosing were only minimally lower than pre-dosing blood pressures. There were no differences between formulations in terms of absolute mean blood pressures and mean decreases from baseline.

Mean heart rates were virtually identical pre- and post-dosing and were not different between formulations.

Laboratory measurements: No laboratory measurements were obtained during this trial.

A.5 Reviewer's assessment of safety and efficacy in this trial:

Overall, the reviewer believes that the results of this study demonstrate that alprostadil sterile powder and alprostadil/ α -cyclodextrin induce comparable erectile responses when administered at comparable doses. This appears true for at-home use as well as for in-clinic administration. Despite the open-label design of this study and the historical control period, these results are compelling.

In terms of safety, there were no new obvious safety concerns noted in the alprostadil/ α -cyclodextrin group compared to the alprostadil sterile powder group. Certainly, this conclusion is limited by the following study deficiencies: a relatively small number of patients, the open-label study design, and the lack of any laboratory measurements or systematic assessments of penile pain.

Despite its limitations, the results of the study did meet its primary objective; specifically, alprostadil/ α -cyclodextrin appears to be "pharmacodynamically bioequivalent" to alprostadil sterile powder.

See page 10 of the Medical Officer review for a review of the Safety Update Report.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-212 Amendment

Medical Officer's Review of Complete Response to Approvable Letter

Date submitted: December 10, 2001

Date received: December 12, 2001

MOR complete: May 10, 2002

Sponsor: Pharmacia & Upjohn

Drug product: Alprostadil for injection

Proposed tradename: Caverject Impulse™

Dosage strengths: 10mcgs and 20mcgs

Indication: Treatment of erectile dysfunction

1. Clinical and regulatory background:

Intracavernosal pharmacotherapy is the direct injection of vasoactive medications into the penile corpora for purposes of inducing an erection in men with erectile dysfunction (ED). Currently, the only approved drug substance for this purpose is alprostadil. The currently approved drug products are Caverject Sterile Powder, Caverject Aqueous, and Edex.

On January 20, 2000, Pharmacia submitted NDA 21-212 for "CAVERJECT DC" a new formulation of alprostadil for intracavernous pharmacotherapy of ED. The application described a lyophilized formulation designed to be of a small enough volume to fit into one chamber of a dual chamber syringe. The dual-chamber syringe would be more convenient for product reconstitution and administration by the patient. The lyophilized powder would provide a longer shelf-life.

On November 20, 2000, the Division issued an approvable letter. The approvable letter contained three numbered "approvable" items, all related to CMC deficiencies. In addition, the sponsor was informed that satisfactory inspections for manufacturing facilities were required prior to approval.

Clinically, the sponsor was told to:

1. Provide revised draft labeling (Division recommended labeling attached to letter)
2. Provide updated safety information about the product.

Finally, the ~~tradename~~, Caverject DC was found unacceptable by the OPDRA and by the Division and therefore the sponsor was asked to submit a new tradename.

On December 10, 2001, Pharmacia submitted a Complete Response to Approvable Letter in the form of an ~~amendment~~ to NDA 21-212. In terms of clinical material for review, this amendment contains the following items:

1. Attachment 3: Revised Insert Labeling
2. Attachment 5: Updated Safety Information, including the final study report for one completed clinical trial (Study 136-URO-0089).

In addition, the amendment makes reference to serial submission #122 to _____, in which additional information was submitted to support the proposed tradename CAVERJECT IMPULSE™.

This reviewer performed a primary medical review of Attachment #3, Attachment #5 and Serial #122 to [REDACTED]

2. Review of clinical material

2.1 Updated safety information (Attachment #5 including Final Report of Protocol 136-URO-0089).

2.1.1. The clinical safety update

This 10-page document summarizes all relevant safety data since September 2000. The sponsor believes that no new safety concerns have been identified with the new formulation, alprostadil alph-cyclodextrin. They believe that the safety profile of alprostadil alph-cyclodextrin remains similar to that for the approved Caverject Sterile Powder.

The 10-page document contains a 9-page summary of Protocol 136-URO-0089 (see below) and one paragraph about adverse events from other sources (Section 8.8.3). Section 8.8.3 states that Caverject Dual Chamber has been marketed in the U.K. since June 2001. The sponsor states that there have been no new safety concerns identified in postmarketing adverse reports for the new product. The sponsor states that there have been new safety concerns identified for Caverject Sterile Powder either. Since the last safety update for Caverject Sterile Powder (February 2000), the sponsor states that [REDACTED] Caverject prescriptions have been written worldwide (an interval of approximately 21-22 months) with no safety concerns identified from postmarketing adverse event reports.

2.1.2. Final Report of Protocol 136-URO-0089

Protocol 136-URO-0089 was an in-office, open-label, non-comparative, dose-titration study of 3-6 weeks duration. The study was conducted from April 2001 to June 2001 at seven centers in India. After appropriate screening, all patients received a single injection of 2.5 micrograms in the office. If a patient was classified as severe vasculogenic ED, then 10 micrograms was used as the starting dose. Subsequently, alprostadil was titrated to the dose producing an effective response (an erection sufficient for intercourse lasting at least 20 minutes). Titration was conducted no sooner than three days after the last dose. At each dose, patients were observed for at least two hours (or one hour if there was no response). During that time, vital signs were monitored pre-dose, 60 minutes after dosing and prior to discharge.

Reviewer's comment: For this study, the drug product was supplied as the dual chamber glass cartridge assembled as a single-unit disposable delivery device. Although previous clinical information has been submitted and reviewed for the lyophilized formulation, this submission provides the first clinical data with the entire delivery device.

Overall, 126 of 127 patients completed the study. Of 127 patients, 118 (93%) were classified as responders. The mean age was 36 years (range 18 to 71). Approximately 50-55% of patients were classified with psychogenic-only ED. Approximately 18% were smokers. Seventy-two percent (72%) of patients started at 2.5mcg. The remainder began at 10mcg. A total of 220 injections were given (92 injections of 2.5 mcg, 39 injections of 5 mcg, 55 injections of 10 mcg, 21 injections of 15 mcg, and 13 injections of 20 mcg).

Reviewer's comments

1. This is an unusual group of ED patients (especially for intracavernosal pharmacotherapy) in that most patients were young and were described as psychogenic in etiology.
2. Most injections were of 10 micrograms and less. This study provides only very limited data for injections of 15 mcg or 20 mcg.

A total of 42 of the 127 patients (32%) reported a total of 77 adverse events. Of the 42 patients reporting adverse event, 39 reported genital disorders. Sixty of the 77 adverse events were reports of penile pain. In most patients the pain was mild to moderate in severity. Four patients experienced severe pain (2 after injection with 15 mcg, one each after injection of 10 and 20 mcgs).

Adverse events were distributed as follows: after 2.5 mcg, 28 AEs (20 pain); after 5mcg, 11 AEs (9 pain); after 10 mcg, 22 AEs (18 pain); after 15 mcg, 10 AEs (8 pain); after 20 mg, 6 AEs (5 pain).

One event of priapism, lasting 6 hours and 55 minutes, was reported.

There were no deaths, no serious adverse events, and no discontinuations due to AEs.

An examination of pre-and post-dosing vital signs did not reveal any notable findings.

Reviewer's comment: I agree that no new safety concerns associated with the new formulation, alprostadil alpha-cyclodextrin, were noted in this study.

2.2 *Revised draft labeling (Attachment #3)*

I agree with all clinical parts of the sponsor's currently proposed physician insert. For the patient package insert, I have only one comment:

I object to the sponsor's contention that the combination use of CAVERJECT with other medical treatments for impotence is "v — " not recommended (see LINE 649 of the underline/strikeout version). Until there is information to support the safety of such use, the word "v — " must be deleted.

The remainder of the proposed patient package insert is acceptable.

2.3 *Proposed tradename (Serial #122 to _____)*

On May 3, 2001, the sponsor submitted a request for tradename review by OPDRA. The proposed tradename was "CAVERJECT Impulse". On August 8, 2001, that tradename was referred to OPDRA for consultation. On August 24, 2001, OPDRA returned a consult stating:

"From a safety perspective, OPDRA has no objection to the proprietary name 'Caverject Impulse'. However, DDMAC has found the name objectionable from an advertising and promotional perspective."

DDMAC objected to the name because they believed that the modifier "Impulse" makes a misleading claim about the drug product. Specifically, they believe that "Impulse" implies that it

is fast-acting or has an immediate effect and thus, the name would overstate the product's efficacy.

DDMAC also ~~was~~ concerned that doctors may forget or omit "Impulse" and thus confuse Caverject Impulse with the current Caverject product. OPDRA felt that while forgetting the modifier "Impulse" was possible, it would certainly not represent a safety problem since both products are of the same dosage strength and same active ingredient for the same purpose. In addition, sponsor was likely to educate prescribers about differences between the new and old products.

On August 30, 2001, Division informed sponsor that tradename, Caverject Impulse, was unacceptable. On September 14 and October 18, 2001, Division provided detailed comments from OPDRA consult directly to sponsor.

Finally, on November 21, 2001, sponsor submitted serial #122 to _____ containing sponsor's arguments towards keeping the proposed tradename and a letter from Neil M. Davis, PharmD, MS, FASHP, President of Safe Medications Practice Consulting, Professor Emeritus of Temple University School of Pharmacy and Editor-in-Chief of *Hospital Pharmacy*.

Reviewer's comment:

In brief, I disagree with DDMAC's contention that CAVERJECT IMPULSE is unacceptable due to any promotional aspect. Based upon my extensive experience with intracavernosal therapy, I am certain that patients will not be "mislead" about this type of treatment. Injection of medication directly into the penile shaft requires a fair amount of patient-physician interaction and patient commitment. This is not taken lightly by most patients.

I also agree with OPDRA, Pharmacia and Dr. Davis that medication errors are extremely unlikely.

Thus based on the above, the Division has already informed the sponsor that the tradename, Caverject Impulse™, is acceptable.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mark S. Hirsch
5/7/02 01:14:49 PM
MEDICAL OFFICER
This is the primary medical review.

Daniel A. Shames
5/8/02 05:23:49 PM
MEDICAL OFFICER

NDA 21-212

Medical Officer's Memorandum

TO: Susan Allen, M.D., M.P.H., Division Director, HFD-580
FROM: Mark S. Hirsch, M.D., Medical Officer, HFD-580
THROUGH: Dan Shames, M.D. Deputy Division Director, HFD-580
DATE: November 17, 2000
REGARDING: All remaining clinical issues related to NDA 21-212

Summary:

In finalizing my review of this NDA, I find three clinical issues of note:

1. **Tradename:** The tradename CAVERJECT DC has been determined to be confusing and potentially problematic. A standardized testing method by OPDRA revealed a potential for misinterpreting the "DC" suffix as an abbreviation for the word "discontinue". I agree with this potential for medical error.

The sponsor has been informed of our recommendation to change this name. The sponsor is conducting "studies" to decide upon a new tradename. None has been submitted as of today.

It is my understanding that a regulatory decision may be taken at this time despite the lack of a tradename. Therefore, this issue does not impact on my final recommendation at this time.

2. **Clinical site inspections:** The Division of Scientific Investigations has informed the Division that an irregularity was noted at one of the two clinical site inspections. The site investigator was Dr. Talley of San Antonio, Texas. Dr. Talley had enrolled fifteen patients. Of these fifteen, DSI determined that irregularities were noted in the first four patients.

DSI noted that the case report forms (CRFs) for the first four patients revealed that the patients' answers to the baseline IIEF questionnaire (EF domain) had been changed by the investigator. These baseline questionnaires assessed the patient's erectile function during the previous four weeks; the CAVERJECT Sterile Powder treatment period. The patient's original numeric responses were changed to higher scores, thus effectively improving the performance of the Sterile Powder.

When asked about this activity, the site investigator stated that he believed that patients had misunderstood the questions. When he carefully explained each question to those four patients, he believed that their answers were more "accurate".

Although this type of document revision is concerning unto itself, I believe that it has no effective impact on determining the efficacy of the new formulation (CAVERJECT DC). Therefore, it has no effective impact on my final clinical recommendation for approval.

3. **Labeling:** FDA-proposed revised labeling was provided to the sponsor on November 6, 2000. These revisions included minor clinical changes to the PI, but extensive formatting changes to the PPI (as proposed by DDMAC). To my knowledge, there has not yet been a response from the sponsor.

It is my understanding that the Division intends to take an "approvable" action based primarily on deficiencies noted in a manufacturing site inspection. Therefore, there is no real urgency to conclude clinical labeling negotiations at this time. I am simply documenting here that the ~~FDA~~ proposed clinical changes to the PI and PPI still require a response. Thus, final clinical agreement on labeling is pending at this time.

Although these proposed clinical revisions to the PI and PPI are not yet "settled", I do not feel that they are of such importance as to necessitate a change in my final recommendation for approval.

/s/

Mark S. Hirsch
11/20/00 04:06:13 PM
MEDICAL OFFICER

Daniel A. Shames
11/20/00 05:09:39 PM
MEDICAL OFFICER