CHRONIC PROSTATITIS RESEARCH NETWORK (CPCRN)

Proposed Randomized Clinical Trial (RCT) #1

A MULTICENTER, RANDOMIZED CLINICAL TRIAL (RCT) TO EVALUATE THE EFFICACY OF ORAL CIPRO®, ORAL FLOMAX® AND THE COMBINATION OF ORAL CIPRO® & ORAL FLOMAX® FOR THE TREATMENT OF CHRONIC PROSTATITIS (CP)/ CHRONIC PELVIC PAIN SYNDROME (CPPS)

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1 INTRODUCTION

Chronic prostatitis (CP) is a disabling condition affecting an untold number of men of all ages and ethnic origins. As early as 1980, the National Ambulatory Care Survey reported 20 office visits/1,000 men/year for symptoms compatible with prostatitis(1). Although by one estimate, 50% of men will suffer from symptoms of prostatitis at some point in their lives, most symptomatic men do not have bacterial prostatitis, for which the treatment and management is usually successful(2). Therefore, as noted by Krieger *et al*(3), the most common syndromes for men with chronic prostatitis are *idiopathic* (abacterial prostatitis). Depending on the status of the expressed prostatic secretions (EPS), these patients with chronic abacterial prostatitis are classified further as a) nonbacterial prostatitis if the EPS is purulent (leukocyte count elevated) or b) prostatodynia if the EPS is not purulent. To date there is no standardized method of diagnosis and treatment of this condition. As noted recently by Nickel and Sorensen(4), the problems and frustrations found in clinical trials investigating therapies for nonbacterial prostatitis are that

> "our definition of the syndromes is unclear, the etiology is obscure, the relevance of the only objective finding we have (leukocytosis) is unknown, symptoms are highly variable, the natural history of the disease has not been adequately studied and the numbers in most clinical trials, including ours, are small".

They concluded that "since the symptoms are paramount in these patients, evaluation of response can only be achieved by using reproducible and validated symptom evaluation instruments."

Recognizing the importance of addressing problems in the diagnosis and treatment of prostatitis, a National Institute of Diabetes, Digestive and Kidney (NIDDK) Diseases Workshop on Chronic Prostatitis(5) was held in Bethesda, MD on December 7-8, 1995, from which the new consensus working definition and classification of prostatitis syndromes (NIDDK reference standard) for research studies on these diseases and disorders was summarized as follows:

1. *Acute bacterial prostatitis* is an acute infection of the prostate.
2. *Chronic bacterial prostatitis* is a recurrent infection of the prostate.
3. *Chronic nonbacterial prostatitis/chronic pelvic pain syndrome* (CPPS), where there is no demonstrable infection. Subgroups of this class are:
   - *3a) Inflammatory chronic pelvic pain syndrome*, where white cells are found in the semen, expressed prostatic secretions (EPS), or voided bladder urine-3 (VB-3).
   - *3b) Non-inflammatory chronic pelvic pain syndrome*, where white cells are NOT found in the semen, EPS, and VB-3.
4. *Asymptomatic inflammatory prostatitis* (AIP), where there are no subjective symptoms but white blood cells are found in prostate secretions or in prostate tissue during an evaluation for other disorders.

Patients in Categories 1-3 are characterized by chronic pain; however, unlike patients in Category 1 & 2, patients with Category 3 prostatitis do not have any detectable infection of the prostate as determined by conventional microbiological techniques. Abnormalities in the EPS are the primary objective features of Category 3 prostatitis and chronic pain is the primary subjective symptom. The majority of patients with chronic prostatitis are Type 3(3).

The occurrence and persistence of pain as a primary presenting symptom is an important aspect of both diagnosis and outcome evaluation. In the recent review article in *Pain* by Egan and Krieger(6), they note that "chronic abacterial prostatitis is remarkably similar to chronic pain syndromes", and accordingly they make the case for therapy based on multidisciplinary approaches to pain management, rather than the traditional 'organ system' approach. Many therapies have been tried for chronic prostatitis, with a primary focus on improving bladder outlet resistance. However, the general consensus among clinical urology research investigators conducting therapy trials involving chronic prostatitis patients is well reflected in the recent summary of Nickel and Sorensen(4) that

> "more research and larger clinical studies in the nonbacterial chronic prostatitis syndromes are urgently required."

In response to these growing concerns about the diagnosis and treatment of Chronic Prostatitis, the NIDDK funded the Chronic Prostatitis Clinical Research Network (CPCRN), comprised originally of (6) Clinical Research Centers (CRCs) and a Data Coordinating Center (DCC), effective October 1, 1997. In preparation for this first clinical trial, four (4) additional clinical research centers have been added. The primary research questions being addressed by the CPCRN encompass the diagnosis, etiology, natural history and prognosis, and the development of treatment strategies focused on Chronic Abacterial Prostatitis - Chronic Pelvic Pain Syndrome (CPPS). In support of these broad research goals, the CPCRN developed a longitudinal Chronic Prostatitis Cohort (CPC) Study, to which patients are currently being accrued and followed. The group also coordinated the development and validation of a symptom severity index for CPPS. This index, known as the NIH-CPSI, will be used as a primary outcome measure for clinical trials in CP(7). In parallel with the CPC, a series of clinical trials designed to address specific treatment questions, both etiologic and palliative, will be conducted. This protocol represents the first multi-center randomized clinical trial (RCT) to be conducted by the CPCRN.

2 STUDY DESIGN

This CPCRN RCT will utilize a 2 x 2 factorial design with four arms to evaluate: 1) placebo + placebo, 2) placebo + tamsulosin hydrochloride (FLOMAX®) 3) placebo + ciprofloxacin (CIPRO®), and 4) tamsulosin hydrochloride (FLOMAX®) + ciprofloxacin (CIPRO®) as displayed in Figure 1. All participants who meet eligibility criteria at baseline screening will be stratified by clinical center and randomized to one of the four treatment arms. The trial will last a total of 12 weeks. Participants will be treated for 6 weeks and followed for an additional 6 weeks. The primary objectives of this trial are:

Figure 1. 2 x 2 Factorial Design

Placebo + Placebo	**Placebo + FLOMAX®**
Placebo + CIPRO®	**FLOMAX® + CIPRO®**

FLOMAX® 0.4 mg OD
CIPRO® 500mg BID

1. To compare placebo, ciprofloxacin (CIPRO®), tamsulosin hydrochloride (FLOMAX®), and the combination of ciprofloxacin (CIPRO®) plus tamsulosin hydrochloride (FLOMAX®) with respect to efficacy endpoints in CP participants

including the NIH-CPSI, participant assessment of global improvement, and other laboratory and clinical outcome measures.

2. To evaluate the safety and tolerability of ciprofloxacin (CIPRO®), tamsulosin hydrochloride (FLOMAX®), and the combination in CP participants.

2.1 Study Time Frame

Approximately 184 participants, 46 per treatment arm, will be treated and followed for a total of twelve (12) weeks. The total time required for this trial will be approximately fourteen (14) months.

2.2 Study Organizations

The CPCRN consists of ten (10) clinical centers that will recruit participants for the RCT. All participants previously enrolled in the CPC will be offered RCT participation if trial eligibility criteria are met. Over 420 participants have been enrolled in the CPC as of March 31, 2001. The target accrual of participants is approximately 18-20 participants at each of the ten (10) clinical centers, resulting in 184 participants. It is expected that each clinical center will accrue participants at the rate of 2-3 participants per month, thus approximately ten (10) to twelve (12) months will be required for accrual. The ten (10) Clinical Centers that will enroll participants into the RCT are:

1. Brigham and Women's Hospital & Massachusetts General Hospital, Harvard University Medical School, Boston, MA 02115
2. Temple University Hospital, Temple University, Philadelphia, PA 19140
3. University of Maryland Medical System, University of Maryland School of Medicine, Baltimore, MD 21201
4. Northwestern University Medical School, Northwestern University, Chicago, IL 60611
5. Harbor - UCLA Medical Center, University of California at Los Angeles, Los Angeles, CA 90024
6. Kingston General Hospital, Queen's University, Kingston, Ontario, Canada K7L 2V7
7. University of Mississippi Medical Center, Jackson, MI, 39216
8. Cleveland Clinic Florida, Weston, FL 33331
9. MLK Drew Medical Center, Los Angeles, CA 90059
10. University of Arizona, Tucson, AZ 85721

2.3 Study Endpoints

2.3.1 Primary Endpoint

The primary endpoint to be used for efficacy evaluation is the overall NIH-CPSI (Appendix A) (scale of 0-43). The change in this score from baseline to six (6) weeks will be calculated for each participant and compared among treatment groups (see Section 10.3 for details of primary endpoint analysis).

2.3.2 Secondary Endpoints

A number of secondary outcome measures related to both specific symptoms and overall symptom scores will be used to supplement the analysis based on the primary endpoint. One secondary endpoint will be a participant-reported global response assessment (GRA) at six (6) weeks or withdrawal; whichever comes first, relative to overall baseline symptoms. Additional symptom-related outcome measures include the NIH-CPSI subscales and MOS SF-12.

Laboratory measures to be followed include WBC in EPS. While the true significance of WBC count in the EPS has yet to be established, it nevertheless is the primary marker of intraprostatic inflammation that can be obtained non-invasively. The exact cutoff point for deciding that inflammation is present is also controversial, with most authors relying on 10 WBC per hpf in a wet mount sample. While many investigators have pointed out the variability of WBC count in participants with CPPS over time,(8) fluctuations in the short term, such as for durations contemplated in this study, are less of a problem(9).

3 STUDY AGENTS

3.1 Ciprofloxacin (CIPRO®)

Despite the fact that most urologists do not perform bacteriologic localization studies(10), the most common therapy for chronic prostatitis is antibiotics(11) and the most common antibiotic in use is ciprofloxacin. The advantages of ciprofloxacin are 1) excellent penetration into the prostate(12), 2) broad spectrum coverage of typical uropathogens as well as chlamydia and 3) high rates of bacterial eradication in participants with chronic bacterial prostatitis(13;14). The most common justification for treating CP participants with antibiotics is the belief that many of these participants have an infection due to cryptic or difficult to culture microorganisms. Indeed, culture of prostatic biopsy tissue in men with negative prostate fluid culture often demonstrates bacteria(15) and bacterial DNA can be isolated from prostate fluid(16) or prostate tissue(17) in a significant proportion of men with culture negative prostatitis. Whether bacteria detected in this manner represent true infection or colonization that is unrelated to symptoms is an issue that has still not been settled.

An alternate explanation for the symptomatic improvement that some CPPS participants achieve with ciprofloxacin could be its direct anti-inflammatory effect. Men with CPPS have documented elevations of inflammatory cytokines such as IL-1, IL-8 and TNF in their prostate fluid(18) and semen(19) as well as elevations in markers of oxidative stress(20). Interestingly, quinolones such as ciprofloxacin have been shown to directly inhibit IL-1 and IL-8 expression from in vitro studies(21;22). Successful treatment with antibiotics also lowers the level of prostatic oxidative stress(20). **(See Appendix D)**.

Considering the prevalence of antibiotics as a treatment agent for men with chronic prostatitis and potential mechanisms effect, the objective of this study is to determine a definitive answer to the question of whether this treatment should be considered a guideline for standard therapy for chronic prostatitis.

Studies of quinolones in men with CPPS suggest that if an impact on symptoms is seen, the effect is detected by four (4) weeks (J. Nickel, personal communication). Therefore we believe that six (6) weeks of therapy should be sufficient to detect an improvement.

3.2 Tamsulosin Hydrochloride (FLOMAX®)

Alpha-blockers are some of the principal treatments for lower urinary tract symptoms due to benign prostatic hyperplasia (BPH). Since some of the symptoms of chronic prostatitis / chronic pelvic pain syndrome are similar to those of BPH, it has been postulated that alpha-blockers may be useful in the treatment of these conditions. Rosette examined the use of the alpha-blocker alfuzosin in men with chronic pelvic pain syndrome(23). In a double blind, placebo-controlled trial, there was no statistically significant difference in reduction in symptoms between men treated with alfuzosin and with placebo. There was, however, a significant difference between treated men and controls in terms of maximal urine flow. Duzendorfer in a similar trial using phenoxybenzamine, however, did find statistically significant improvements in several pain outcomes at six (6) weeks in treated participants compared to controls(24). The treatment group complained of orthostatic changes, which are not unknown in the use of alpha-blockers, but more "uroselective" alpha-blockers now likely reduce these potential side effects. Other studies have also looked at alpha-blockers, principally phenoxybenzamine, and have shown symptomatic improvement in approximately 50% of participants.

Tamsulosin hydrochloride (FLOMAX®) is a newer alpha-adrenergic blocking agent, which has been used extensively for the treatment of BPH. It is a methoxybenzene sulfonamide with a chemical structure that differs from second generation alpha-blockers such as prazosin and alfuzosin, which are quinazoline derivatives. Since it is an alpha 1A selective antagonist, dose titration is not necessary. There is little effect on blood pressure, which improves its overall tolerability. In clinical trials in the treatment of BPH, efficacy as measured by improvement in voiding symptoms and peak flow rates has been reported as significant compared to placebo(25;26). First dose orthostatic effects were rare and there were no significant ECG effects. **(See Appendix E)**.

3.3 Combination of Ciprofloxacin (CIPRO®) and Tamsulosin Hydrochloride (FLOMAX®)

The etiology and pathogenesis of pain and voiding dysfunction in men with CPPS are not known and are likely multi-factorial. For instance, chronic infection may lead to irritation of muscles at the bladder neck, which might persist even after eradication of the infection. Alternatively, recurrent infection may be caused by persistence of residual urine in men with dysfunctional voiding. The rationale for the combination of ciprofloxacin and tamsulosin hydrochloride therefore is to 1) attempt to maximize eradication of bacteria by improving bladder emptying, 2) improve both pain and voiding symptoms, regardless of etiology and 3) gain insight into the pathophysiology of CPPS by comparing pretreatment culture and voiding parameters with response to medications.

In a retrospective, nonrandomized study, the combination of alpha blockers and antibiotics were superior to antibiotics alone in men with chronic bacterial prostatitis(27). For men with nonbacterial prostatitis, alpha-blockers were superior to antibiotics for improving symptoms. The combination of agents was well tolerated with no unique side effects seen. Indeed, there is

no mechanistic reason to suppose that a fluroquinolone such as ciprofloxacin would interact with a selective alpha-1 blocker such as tamsulosin hydrochloride.

With regard to the pathogenesis of symptoms, one hypothesis to be tested is whether participants with urinary symptoms plus pain are somehow different from those with pain alone. If participants with pain alone, without voiding symptoms, respond to tamsulosin hydrochloride in the same way those with voiding symptoms, then the beneficial actions may be centrally mediated. If only participants with voiding symptoms respond to tamsulosin hydrochloride, then the action may be either central or at the end organ level. Similarly, it will be important to correlate any response to ciprofloxacin (CIPRO®) with the presence of bacterial growth in the prostate or urine for micro-organisms, especially bacteria considered to be "non-pathogens" such as gram positive bacteria. If eradication of bacteria is associated with an improvement of symptoms, then a pathogenic role is suggested. If improvement is seen regardless of culture status, then a direct anti-inflammatory role of the antibiotic would be likely.

4 PARTICIPANT CRITERIA

4.1 Study Population

The study population of particular interest is the group of male participants with symptomatology consistent with Chronic Prostatitis (CP) or Chronic Pelvic Pain Syndrome (CPPS). Each potential study participant must meet the following set of eligibility criteria in order to be entered in the RCT.

4.1.1 Inclusion Criteria

1. Participant has signed and dated the appropriate Informed Consent document.
2. Participant is a male.
3. Participant must have had symptoms of discomfort or pain in the pelvic region for at least a three (3) month period within the last six (6) months.
4. Participant has at least a moderate overall score on the NIH-CPSI (overall score ≥ 15 out of a potential of 0 – 43 points).

4.1.2 Exclusion Criteria

Any participant satisfying any one of the following criteria will **NOT** be eligible to participate in the RCT.

1. Participant has a history of prostate, bladder or urethral cancer.
2. Participant has inflammatory bowel disease (such as Crohn's disease or ulcerative colitis, but not irritable bowel syndrome).
3. Participant has undergone pelvic radiation or systemic chemotherapy.
4. Participant has undergone intravesical chemotherapy.
5. Participant has been treated with intravesical BCG.
6. Participant has been treated for unilateral orchialgia without pelvic symptoms.
7. Participant has an active urethral stricture.
8. Participant has a neurological disease or disorder affecting the bladder.
9. Participant has undergone TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment such as cryotherapy or thermal therapy.
10. Participant has a neurological impairment or psychiatric disorder preventing his understanding of consent and his ability to comply with the protocol.
11. Participant has liver disease.
12. Participant has a known allergy or sensitivity to ciprofloxacin hydrochloride (CIPRO®), tamulosin hydrochloride (FLOMAX®) or any of their known components.
13. Participant has a history of seizure disorder.
14. Participant is taking theophylline, phenytoin, probenecid or warfarin.
15. Participant requires ongoing use of magnesium, aluminum, or calcium-containing antacids.

4.1.3 Deferral Criteria

For some conditions, participants may be reconsidered for entry into the trial once the condition has resolved as indicated below.

1. Participant has been treated with tamsulosin hydrochloride (FLOMAX®), doxazosin mesylate (Cardura®), terazosin HCL (Hytrin®), or alpha-blockers in the past four (4) weeks.
2. Participant has been treated with ciprofloxacin hydrochloride (CIPRO®) in the past four (4) weeks.
3. Participant has been treated with antimicrobial agents (oral or parenteral) in the past four (4) weeks.
4. Participant has started, stopped, or changed dose level of **ANY** prostatitis-specific medications within the past four (4) weeks.
5. Participant has had a urinary tract infection, with a urine culture value of >100,000 CFU/ml, within the past three (3) months.

6. Participant has had clinical evidence of urethritis, e.g. including urethral discharge or positive culture, within the past three (3) months, diagnostic of the following sexually transmitted diseases (STDs): gonorrhea, chlamydia, mycoplasma or trichomonas, but not including HIV/AIDS.
7. Participant has had a prostate biopsy in the past three (3) months.
8. Participant has experienced symptoms of acute or chronic epididymitis within the past three (3) months.
9. Participant has begun finasteride (Proscar®) or other androgen hormone inhibitors in the past six (6) months, or stopped finasteride (Proscar®) or other androgen hormone inhibitors within the past six (6) months.
10. Participant has used bioflavonoid agents [Example: Quercetin] in the past two (2) weeks.
11. Participant has been diagnosed with or treated for symptomatic genital herpes in the past twelve (12) months.
12. Participant has been taking zinc or iron supplements within the past two (2) weeks.
13. Participant has been treated with cimetidine in the past two (2) weeks.

5 PARTICIPANT RECRUITMENT AND CONSENT

5.1 Risks and Benefits to Participants

This is a double-masked, placebo-controlled RCT evaluating the efficacy and safety of ciprofloxacin (CIPRO®) and tamsulosin hydrochloride (FLOMAX®) in participants with CP. After evaluation of previous study data and physician participant records using these drugs, it is anticipated that there may be a direct benefit to the participants, however, direct benefits are not guaranteed. The information gained from this study may eventually prove beneficial to the treatment and diagnosis of other CP participants. Potential risks to the participants are limited to risks related to venipuncture and the use of the study drugs.

5.2 Risks of Ciprofloxacin (CIPRO®)

Ciprofloxacin is a synthetic fluoroquinolone antimicrobial agent with a broad spectrum of activity against aerobic bacterial organisms. The principal risks of ciprofloxacin use are as follows:

- Hypersensitivity to ciprofloxacin can occur. This can result in skin rashes or even severe anaphylactic reactions even after a single dose. Such severe reactions are very rare but participants should discontinue the drug if a skin rash or any other evidence of sensitivity to the drug occurs.
- Pseudomembranous colitis can occur after treatment with ciprofloxacin, as with most antimicrobial agents. This can result in severe diarrhea due to overgrowth of *Clostridium difficile* in the colon because of the removal of normal bacterial flora by ciprofloxacin. Participants should contact their physician if persistent diarrhea occurs after taking the drug.

- Ciprofloxacin can cause hypersensitivity to sunlight. Participants should avoid excessive exposure to sunlight or ultraviolet light while taking the drug. The drug should be discontinued if phototoxicity, such as sunburn, occurs.
- Central nervous system effects can occur with ciprofloxacin, including lightheadedness, dizziness, nervousness, anxiety, agitation, insomnia, nightmares or paranoia. Rarely, seizures or convulsions have been reported in participants taking ciprofloxacin. A history of seizure disorder should be reported to the physician prior to instituting therapy with ciprofloxacin.
- Ciprofloxacin may increase the effect of caffeine or the drug theophylline, used for asthma. Caffeine should be used with caution in the participant taking ciprofloxacin and the concomitant use of theophylline and ciprofloxacin may require dosage modification of theophylline.
- Rarely, participants taking ciprofloxacin have developed problems with tendons, including rupture or spontaneous tendon injury. Participants taking ciprofloxacin should discontinue the drug at the first sign of inflammation, pain or rupture of a tendon. If this occurs they should also rest, refrain from exercise and report the event to their physician immediately.

5.3 Risks of Tamsulosin (FLOMAX®)

Tamsulosin is a synthetic antagonist of the $alpha_{1a}$ adrenergic receptor in humans.

- Hypersensitivity to tamsulosin can occur. This can result in skin rashes, pruritis, urticaria or angioedema. Participants with a known hypersensitivity to tamsulosin or any component of the drug formulation should be excluded.
- The principal risk of alpha adrenergic blockers is a lowering of blood pressure while on the drug. This can result in dizziness, syncope or postural hypotension. In the U.S studies of tamsulosin, symptomatic postural hypotension occurred in 1 of 502 men receiving 0.4 mg/day (0.4%) compared to none of 493 men receiving placebo. Participants should be warned of the risk of dizziness, lightheadedness or syncope when taking tamsulosin.
- Ejaculation abnormalities are associated with the use of tamsulosin. These include anejaculation, retrograde ejaculation or decrease in ejaculate volume. This was reported in 8.4% of men receiving 0.4 mg/day tamsulosin and 0.2% of men receiving placebo. In rare cases (less than 1 in 50,000) tamsulosin has been associated with priapism.
- Cimetidine can increase the level of tamsulosin. There are no other reported significant drug interactions.

5.4 Participant Recruitment

Participant recruitment will be conducted through the urology clinic at each of the participating Clinical Research Centers (CRCs). Participants referred to the CRCs with symptoms suggestive of CP/CPPS will be introduced to the RCT by the Research Coordinator and by a participant recruitment brochure describing the study **(See Appendix G).** In addition, a participant recruitment video, which also describes the study and participation requirements, has been developed for use by the ten participating clinical centers **(See Appendix H).** In an effort to

recruit minority participants, network clinical centers will seek the participation of primary care physicians, clinic centers, and other referral sources not previously included in the CPCRN. Potentially eligible participants will then be asked whether they are interested in participating in the study. The study will identify participants by referral source and zip code in order to more fully describe the study population.

5.5 Participant Selection

Initially every potential study participant will undergo a series of screening procedures that take approximately 2 - 3 weeks to complete. The screening phase entails at least two clinic visits. The screening process may take three visits, depending on procedure completion. The data collected and diagnostic procedures completed during this phase are identified in Sections 7.2 and 7.3, in the order in which they will be obtained or undergone. The order of the procedures has been selected to ensure that eligibility criteria checked by non-invasive methods precede those checked by more invasive methods, and to provide a balance of participant comfort and timeliness.

5.6 Informed Consent

Each clinical center will prepare an informed consent form following the guidelines of their local Institutional Review Board and applicable regulations for Informed Consent. The form will, at a minimum, contain a description of the potential risks, benefits, expense to the subject, and alternative treatment. The basic elements of the proposed informed consent are in **Appendix B**.

If the participant expresses interest in participating, he will be asked to sign and date the informed consent form. This form will provide consent for both the screening procedures and the follow-up procedures. Prior to signing the informed consent, the Research Coordinator will review the details of the consent form orally with the participant, and answer any questions that the participant has concerning participation in the RCT. The original signed consent form will be kept in the participant study file at the clinical center, while a copy of the signed consent form will be given to the participant.

6 TREATMENT PROCEDURES

Participants meeting all eligibility criteria will be randomized electronically to one of the four treatment arms. Each participant will receive a 6 (six)-week supply of tablets containing ciprofloxacin (CIPRO®) (or its matching placebo), and a 6 (six)-week supply of capsules containing tamsulosin hydrochloride (FLOMAX®) (or its matching placebo). The study medications will be provided in tamper evident sealed bottles, and will be labeled according to regulatory requirement per Code of Federal Regulations (CFR), Title 21, Part 312.6.

The Research Coordinator will provide explicit instructions to the participant at the time of randomization and dispensing of study drugs. The participant will be instructed that if at any time he should miss a daily dose, he should take the next dose at the usual time. The participant may not “double-up” a dose. The participant will be instructed to save the containers, even if they are empty, and return all study medications at each follow-up visit, to assist the study in compliance monitoring.

6.1 Ciprofloxacin (CIPRO®)

6.1.1 Dosing Schedule

The prescribed dose for ciprofloxacin (CIPRO®) is 500 mg twice a day (BID). The preferred time for dosing of ciprofloxacin is two hours after meals. Ciprofloxacin can be taken with or between meals. The drug should not be taken with milk or yogurt alone, however, because dairy products can decrease the absorption of ciprofloxacin. In addition, the use of antacids containing magnesium, aluminum or calcium and supplements containing iron or zinc can decrease the absorption of ciprofloxacin and should be avoided while taking the drug.

6.1.2 Drug Manufacturing and Packaging

Ciprofloxacin (CIPRO®) is manufactured by Bayer Corporation (West Haven, CT). Bayer Corporation will supply Ciprofloxacin (Cipro®) directly to the University of Pennsylvania Investigational Drug Service (IDS).

6.1.3 Placebo for Ciprofloxacin

The placebo tablets which are manufactured by Bayer Corporation, and are identical to Ciprofloxacin (Cipro®) tablets, will be shipped directly to the University of Pennsylvania Investigational Drug Service and will be taken on the same twice a day schedule (BID). Placebo for Ciprofloxacin (Cipro®) will be packaged and labeled identically to Cipro® tablets.

6.2 Tamsulosin Hydrochloride (FLOMAX®)

6.2.1 Dosing Schedule

The dose of tamsulosin hydrochloride (FLOMAX®) for this study is 0.4 mg daily, which is taken once a day (OD), 30 minutes following a meal. This dose is presently approved in the United States for the treatment of urinary symptoms related to benign prostatic hyperplasia. No dose titration is required.

6.2.2 Drug Manufacturing and Packaging

Tamsulosin hydrochloride (FLOMAX®) is manufactured by Yamanouchi Pharmaceuticals Co., Ltd. (Tokyo, Japan) and is distributed by Boehringer Ingelheim Pharmaceuticals, Inc.. Boehringer Ingelheim Pharmaceuticals, Inc. will supply Tamsulosin hydrochloride (FLOMAX®) directly to the University of Pennsylvania Investigational Drug Service.

6.2.3 Placebo for Tamsulosin Hydrochloride (FLOMAX®)

The placebo tablets which are manufactured by Yamanouchi Pharmaceuticals Co., Ltd. (Tokyo, Japan) and is distributed by Boehringer Ingelheim Pharmaceuticals, Inc., and are identical to tamsulosin hydrochloride (FLOMAX®) capsules, will be shipped directly to the University of Pennsylvania IDS and will be taken on the same once a day schedule (OD). Placebo for tamsulosin hydrochloride (FLOMAX®) will be packaged and labeled identically to (FLOMAX®) capsules.

6.3 Concomitant Medications

6.3.1 Exclusionary Medications

Participants will be monitored at each clinic and phone visit as to their use of over the counter and prescription medications. During the course of the study, the participant **MAY NOT** initiate or otherwise consume any of the following medications:

1. Tamulosin hydrochloride (FLOMAX®) other than study drug.
2. Ciprofloxacin (CIPRO®) other than study medication.
3. Terazosin HCL (Hytrin®) or doxazosin mesylate (Cardura®).
4. Antimicrobial agents.
5. Finasteride (Proscar®), or other 5-alpha reductase inhibitors, unless taking at baseline. (Note: If the participant is taking one of these medications at baseline, he should continue taking these for the duration of the study.)
6. Warfarin (Coumadin®).
7. Phenytoin (Dilantin®).
8. Probenecid (Benemid®).
9. Antacids.
10. Zinc Supplements.
11. Bioflavonoids (i.e. Quercetin).

7 TRIAL TESTS AND PROCEDURES

7.1 Procedural Summary

Prior to the baseline screening, potential participants must have had symptoms of discomfort or pain in the pelvic region for at least a three (3) month period within the last (6) months.

This study is comprised of phases for each participant: i) the *screening phase* and ii) *the treatment and follow-up phase*. The screening phase, which assesses a participant's eligibility via inclusion, exclusion and deferral criteria, will consist of two baseline visits no more than three (3) weeks and no less than seven (7) days apart. Any candidate failing any of the inclusion or exclusion criteria, during either of the screening visits will be considered ineligible for the protocol. Some participants may have their entry into the study deferred to a later time based on the results of the deferral criteria.

7.2 Screening Visit #1

The first screening visit should occur no more than three (3) weeks and no less than one (1) week prior to randomization. During this screening visit, the forms and procedures listed below will be completed. If a participant fails to meet any of the study eligibility criteria, based on the data collected during this visit, he would not be required to complete the physical examination, urinalysis, or urine culture for the purposes of the study. **(See Appendix C)**.

1. *Eligibility Criteria*.

Each participant will complete a preliminary screening form that checks whether he meets the initial inclusion/exclusion/deferral criteria. (These criteria will be verified at the second baseline visit.)

2. *Participant Contact Information*.

Participants will be asked to provide the clinical center with their address, phone number, primary care physician, and the name and address of two other contacts. This information will be stored at the CRC and available only to selected study personnel. Participants who have previously enrolled in the CPC will be asked only to update the previous information.

3. *Participant Medical History*.

Each participant will provide the research staff with his general medical history and specific genitourinary medical history. In particular, the participant will be asked to provide information regarding his disease and surgical histories.

4. *Participant Symptom Index*.

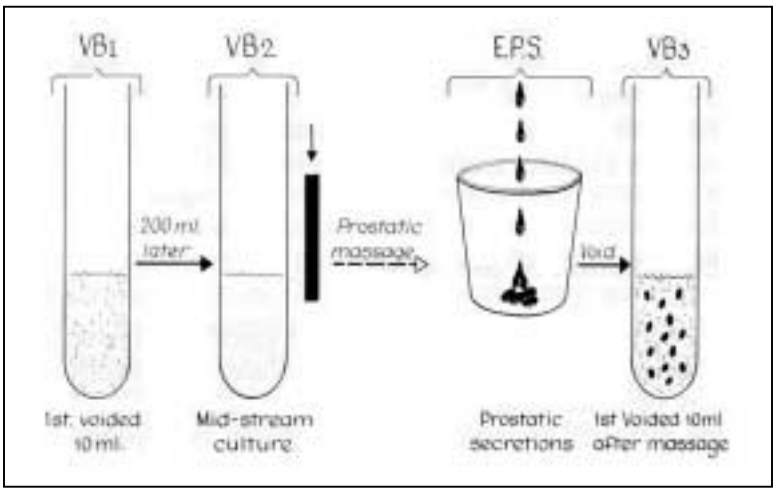
Each participant will provide the research staff with an assessment of his discomfort/pain by completing the full NIH-CPSI.

5. *Physical Examination*.

Each participant will undergo a focused physical examination. This examination will include an abdominal exam, external genital exam, rectal exam, prostate exam, and perineal exam. Participants enrolled in the CPC who have completed a physical examination within one (1) month of enrolling in the RCT, will not be asked to complete another physical examination.

6. *Urinalysis, Urine and EPS Specimens for Microscopy and Culture*.

Each participant will provide the research staff with three (3) urine specimens and an EPS (expressed prostatic secretion) specimen for analysis and culture. The urine specimen will be collected via the classic "four-glass test" (FGT) described in Meares and Stamey(28). The FGT will be attempted one time only at each of Screening Visit #1 and at the six (6) week clinic visit.



The results from the EPS culture and the post-EPS urine (VB_3), if available, will be compared with the findings from the 1st voided urine (VB_1) and the midstream urine (bladder specimen or (VB_2). A macroscopic urinalysis will be completed to quantify hemoglobin, protein, and glucose levels, and a microscopic urinalysis will be completed to quantify white blood cells, red blood cells and yeast. All specimens will be cultured for 5 days. The VB2 culture will also be used to determine UTI status. Although the urinalysis will be performed at the respective CRC, all centers will be required to use the same brand of dipstick. In addition, a portion of the first voided specimen will be tested for chlamydia trachomatis using PCR. (**Appendix F)**.

7. *Next Visit Preparation*.

i. Appointment scheduling. An appointment will be made for Screening Visit #2, to occur no sooner than one (1) week and no later than three (3) weeks after Screening Visit #1.

ii. Concomitant medications. Each participant will receive instructions from the RC to bring to Screening Visit #2 all/or a list of all the over-the-counter and prescribed medications that he is currently taking.

iii. 1-day Voiding Log Supplies and Directions. Each participant will be provided with a voiding log. The participant will be asked to select a typical day, record the date, time and amount of each urination during a complete 24 hour time period. The participant will be asked to return the completed log at Screening Visit #2.

7.3 Screening Visit #2

Participants who still meet all eligibility criteria at this visit will complete the questionnaires and/or undergo the examinations described below, and will continue on to randomization (Section 7.4).

1. *Eligibility Checklist*.

An eligibility checklist confirming that the participant still meets all eligibility criteria will be completed by the RC prior to randomization.

2. *Demographic Questionnaire*.

Each participant will provide the research staff with his demographic information, including date of birth (age), race, marital status, socioeconomic status, level of education.

3. *Concomitant Medications*.

The research staff will record the medications currently being taken by the participant. Participants will be asked to recall their medications if they fail to bring them to the second screening visit.

4. *Participant Symptom/Impact/General Quality of Life Index*.

Each participant will provide the research staff with an assessment of his discomfort/pain by completing the NIH-CPSI. In addition, participants will complete the MOS SF-12, a general Quality of Life Index.

5. *1-day Voiding Log Supplies and Directions*.

A 24-hour voiding log will be collected and reviewed for completion for each participant.

6. *Uroflow and Post Void Residual*.

Participants will undergo urodynamic testing at screening visit #2. The research staff will measure and record participants total voided volume, peak flow, average flow and post-void residual.

7. *Semen Sample Collection*.

A semen sample will be collected and cultured for localized pathogens. Participants are permitted to refuse to provide a semen sample. It is also acceptable if a participant is unable to provide a semen sample. However, participants not providing a semen sample, for whatever reason, must have provided at least one of either an EPS or VB3 sample during screening visit #1.

8. *Medication Diary*.

Participants will be required to maintain a medication diary to record any changes in medication. Participants will also be asked to record all possible adverse events.

7.4 Randomization

If it is determined that the participant meets all eligibility criteria, then randomization to one of the four treatment arms will be implemented. Participants will be randomized in equal proportions to one of the four treatment arms, using a randomized block design stratified by clinical site. At the time of randomization, the participant will be provided with two (2) tamper evident bottles of study medications and thorough instructions on how to take each of them. Details of the participant instructions will be provided in the Manual of Procedures (MOP).

7.5 Week Three (3) Telephone Contact

The Participant contact at week number three (3) post randomization is completed via telephone. During this contact, participants will be instructed to complete, and mail back to the clinical center, self administered forms, as well as answer questions regarding follow-up contacts and adverse events.

Self Administered Forms:

1. NIH-CPSI
2. MOS-SF12
3. Follow-Up Symptoms

Telephone Contact:

1. Follow-Up Contact
2. Adverse Events/Serious Adverse Events

7.6 Week Six (6) Clinic Visit

The Participant visit at week number six (6) will be a clinic visit. At this time, participants complete the following indices or forms as well as undergo the following procedures.

Clinic Visit Indices:

1. NIH-CPSI
2. MOS-SF12
3. Follow-Up Symptoms
4. Follow-Up Contact
5. Adverse Events/Serious Adverse Events
6. Voiding Log
7. Medication Diary
8. Concomitant Medications
9. Treatment Stop Form

Clinic Laboratory Procedures and Physical Exam:

1. Four Glass Microscopy and Culture Test
2. Post Void Residual
3. Physical Examination
4. Semen Sample (collected only if participant has localized uropathogens at baseline. Participant will be scheduled 2-3 days following clinic visit for semen sample collection).

7.6.1 Study Treatment Completion

Each participant will be required at week number six (6) to complete a Treatment Stop Point form. Participants will report any and all reasons for stopping treatment medications prior to week six (6).

7.7 Week Nine (9) and Twelve (12) Telephone Contact

The Participant contacts at week number nine (9) and week number twelve (12) post randomization are completed via telephone. During these contacts, participants complete the following indices or forms:

1. NIH-CPSI
2. MOS-SF12
3. Follow-Up Symptoms
4. Follow-Up Contact
5. Adverse Events/Serious Adverse Events
6. Study Stop Point (***Week Twelve (12) only***)

7.7.1 Rescue Medications

At anytime during the post treatment phase of the trial, participants may use a "rescue medication" for symtoms related to their chronic prostatitis. Participants will receive a packet of forms at their last clinic visit (week 6) with instructions on reporting rescue medication. Participants are required to inform the Research Coordinator when they take any form of a rescue medication.

8 ADVERSE EVENTS AND PARTICIPANT WITHDRAWAL

The Investigator(s) will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, adverse events, or precautions pertinent to the safety of the drug under investigation. Details of adverse events reporting are described below.

8.1 Definitions of Adverse Events (AEs)

An Adverse Event is **ANY** unfavorable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs will be reported to the study investigator and recorded on a case report form.

8.2 Definition of Serious Adverse Events (SAEs)

A serious adverse event is defined as any untoward (unwanted) medical occurrence that at **ANY** dose

- Results in death
- Is life-threatening
- Results in a persistent of significant disability/incapacity
- Results in in-patient hospitalization or prolongation of existing hospitalization
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

8.3 Reporting Obligations for SAEs and IND Safety Reports

The Clinical Site is responsible for reporting SAEs to the DCC within 24 hours of first knowledge of the event via telephone, followed by a facsimile, (which includes both the corresponding **AE Case Report Form** and the **MedWatch** Form). In addition, the site must promptly report all SAEs to their **IRB via written/dated notification** in accordance to the IRB's reporting requirements. Copies of all such correspondence must be maintained in the clinical site's main study binder. All SAEs must be followed with appropriate medical management until resolved.

Upon Notification from the clinical site, the DCC will notify the sponsor (NIH/NIDDK) of SAEs within one (1) working day. Should any SAEs fall into the category of IND Safety Reports (serious, unexpected, and possibly related to drug), the DCC, as designated by the NIH/NIDDK, will report the event to the FDA and all investigational sites in accordance to the process and timelines specified in the FDA regulations. DCC will serve as the sponsor's designee by disseminating the IND safety reports to all clinical sites and promptly notifying the Licensed Product Holders.

8.4 Potential Adverse Events

8.4.1 Ciprofloxacin Hydrochloride (CIPRO®)

During clinical investigation with the tablet, the most frequently reported events, drug related or not, were nausea (5.2%), vomiting (2.0%), abdominal pain/discomfort (1.7%), and rash (1.1%). Most of the adverse events were described as only mild or moderate in severity, abated soon after the drug was discontinued and required no treatment. In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets (500mg BID) to cefluroxime axetil (250

mg-500 mg BID) and to clarithromycin (500 mg BID) in participants with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse event profile comparable to the control drugs.

In several instances nausea, vomiting, tremor, irritability, or palpitation were judged by the investigator to be related to elevated serum levels of theophylline possibly as a result of the drug interaction with ciprofloxacin. Serious and fatal reactions have been reported in participants receiving concurrent administration of ciprofloxacin and theophylline.

Post-Marketing Adverse Events: Additional adverse events, regardless of the relationship to the drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:

- Change in serum phenytoin
- Postural hypotension, vasculitis
- Agitation, confusion, delirium, dysphasia, myoclonus, nystagmus, toxic psychosis
- Constipation, dyspepsia, flatulence, hepatic necrosis, jaundice, pancreatiitis, pseudomembranous colitis
- Aganulocytosis, hemolytic anemia, methemoglobinemia, prolongation of prothrombin time
- Elevation of serum triglycerides, cholesterol, blood glucose, serum potassium
- Myalgia, possible exacerbation of myasthenia gravis, tendinitis/tendon rupture
- Albuminuria, candiduria, renal calculi, vaginal candidiasis
- Anaphylactic reactions, erythema multiforme/Stevens-Johnston syndrome, exfoliative dermatitis, toxic epidermal necrolysis
- Anosmia, taste loss

Adverse Laboratory changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship are listed below:

- Elevated ALT(SGPT), AST(SGOT), alkaline phosphate, LDH, serum bilirubin
- Eosinophilia, leukopenia, decreased blood platelets, elevated blood platelets, pancytopenia
- Elevations of serum creatinine, BUN, crystalluria, cylindruria, hematuria have been reported
- Other changes in <0.1%: elevation of serum gammaglutamyly transferase, elevation of serum amlyase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, leukocytosis

Placebo

Inactive agent—Adverse events not expected.

8.4.2 Tamsulosin Hydrochloride (FLOMAX®)

Adverse events reported in the U.S. and European placebo-controlled clinical trials included: headache in 19%, infection in 9.0%, back pain in 7.0%, chest pain in 4.0%, asthenia in 7.8%, dizziness in 14.9%, somnolence in 3.0%, insomnia in 2.4%, decreased libido in 1.0%, rhinitis in

13.1%, pharyngitis in 5.8%, Increased cough in 3.4%, sinusitis in 2.2%, diarrhea in 6.2%, nausea in 2.6%, tooth disorder in 1.2%, abnormal ejaculation in 8.4% and amblyopia in 0.2%.

In two U.S. studies, symptomatic postural hypotension was reported by 0.2% of participants in the 0.4mg group, 0.4% of participants in the 0.8 mg group and by no participants in the placebo group. Syncope (0.2-0.4%), dizziness (15%), and vertigo (0.6%) were reported on 0.4 mg group and 0.4%, 17%, 1% on 0.8 mg, respectively.

Post-Marketing Experience: Allergic type reactions such as skin rash, pruritus, angioedema of tongue, lips and face and urticaria have been reported with positive rechallenge in some cases. Priapism has been reported rarely. Infrequent reports of palpitations, contipation and vomiting. Latest dated Package Insert (November, 1999).

Placebo

Inactive agent—Adverse events not expected.

8.5 Unmasking of Treatment

At the end of Baseline Screening Visit #2, participants will be randomized following a randomization schedule generated by the DCC prior to study initiation. Neither the Investigator nor the investigational site personnel will know the treatment group to which any participant is randomized. Unmasking of treatment assignment is anticipated to be an extremely uncommon occurrence and is strongly discouraged. If there is a serious adverse event, which is thought by the clinical site staff to be possibly or probably related to the coded medication, the clinical site staff, when necessary for the safety of the participant, may be permitted to request unmasking of treatment group assignment. Approval to unmask will be granted by the study's medical monitor in collaboration with the clinical site's Investigator.

The clinical site staff should contact the On Site Investigator, who would promptly page the medical monitor. If decided that unmasking is appropriate, the medical monitor should immediately contact the University of Pennsylvania Investigational Drug Service (IDS) with a request to unmask the treatment group assignment. The IDS Pharmacist will report the treatment arm to the On Site PI (or designee). The clinical site staff must report the unmasking to the DCC via within one (1) working day, to be followed by submission of a detailed report to the DCC within three (3) working days of the unmasking event. The clinical site must also promptly notify their IRB of the unmasking occurrence in accordance to reporting requirements.

In accordance to the ICH *Guideline for Industry Clinical Safety Data Management's* section on expedited reporting: "Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse event is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion." For the purposes of this protocol, if dissemination of this unmasking information from the Sponsor to the Licensed Product Holders is requested, a collaborative discussion/process is appropriate.

8.6 Participant Withdrawal

It is expected that up to 10% of participants may drop out of the trial due to side effects or lack of efficacy prior to the six (6) week endpoint. However, all attempts will be made to get complete data on all participants, including those who cease treatment prior to six (6) weeks, in order to conduct the primary intent-to-treat analysis. It is expected that a maximum of 15% of participants will withdraw completely from treatment AND follow-up prior to six (6) weeks.

Under certain circumstances, a study participant may have his treatment terminated prior to the six (6) week clinic visit. These circumstances include: unacceptable concomitant medications/treatments, unacceptable adverse events as determined by the Principal Investigator (PI), participant dissatisfaction with treatment, or participant disinterest in continued study participation. In addition, any participant who acquires a serious or life-threatening medical condition while participating in the study may have the study treatment terminated early at the discretion of the PI. A participant may also undergo early study termination because of a change of residence outside the driving distance of the CPCRN network.

9 ADMINISTRATIVE RESPONSIBILITIES

9.1 Institutional Review Board

It is the responsibility of the Principal and Co-Investigator(s) at each site to provide the appropriate Institutional Review Board (IRB) with all pertinent material, including a copy of the informed consent. Approval of the protocol and the informed consent form must be obtained and forwarded to the sponsor prior to screening or enrolling any subjects.

The Investigator also maintains the responsibility of initiating protocol re-approval, notification of protocol and/or consent form changes, notification of adverse reactions, and termination of the study according to the appropriate IRB requirements. A sample consent form is included in **Appendix B.**

9.2 Laboratory Accreditation

The Principal and Co-Investigator(s) must maintain documentation of adequate licensure or accreditation for all clinical laboratory facilities used for study sample analysis. In addition, the clinical laboratory's normal values for test results must be forwarded to the DCC prior to study initiation and annually thereafter. This documentation should cover the entire period the protocol is active.

9.3 Sponsor Monitoring/On-site Monitoring

The DCC has developed written standard operating procedures (SOPs) to ensure that all aspects of the randomized clinical trial are conducted in a standard and uniform manner. These procedures will be organized into a Manual of Procedures (MOP), which will comply with the protocol, GCP and applicable regulatory requirements. All study associated personnel will be trained in study conduct and procedures prior to the start of the trial. A data and safety monitoring plan and data-monitoring schedule will be developed to assess protocol adherence. This plan will be presented to the External Advisory Committee for approval for implementation.

9.4 Compliance with Agencies

The sponsor will ensure that this study is performed in compliance with applicable regulations associated with the Food and Drug Administration (FDA), the International Conference on Harmonization (ICH), (29) and the Declaration of Helsinki. The sponsors will also keep a 1572 (Statement of Investigator), and current CVs of all Principal Investigators and Research Coordinators on file.

9.5 Record Retention

The DCC must maintain all trial records for a period in accordance with their internal Standard Operating Procedures (SOP) and applicable regulations.

9.6 Direct Access to Source Documents

Investigators will maintain, on-site, in an orderly fashion, for a period of no less than seven (7) years, and make available to the sponsor or the sponsor's representative, the following documents: the signed study protocol, amendments, informed consent documents, investigator brochure, approval letters from the IRB, drug accountability forms, CRFs, all primary source documentation, and all letters of correspondence.

9.7 Data Management and Quality Assurance

The Data Coordinating Center (DCC) will coordinate all study activities pertaining to:

1. Design, development, production, testing and distribution of case report forms (CRFs) over the internet to the client workstations at each clinical center;

2. Collection, entry, verification, validation and query resolution of data; and

3. Quality Assurance monitoring and reporting.

Data management issues, especially those concerning data quality and integrity in multi-center trials, as discussed extensively in Meinert (30) DeMets (31) Neaton (32) Bailey (33), and McFadden (34), will be addressed within the Manual of Procedures (MOP) and emphasized during the Research Coordinator (RC) training prior to protocol initiation.

The DCC will develop and maintain a computerized Data Management System (DMS) for this Protocol that will be deployed over the WORLD WIDE WEB using standard Web Browser tools within each of the Clinical Centers. Case report forms (CRFs) will be available to be printed locally at the clinical centers from Portable Document Files (PDF). Originals of these forms will be retained by the clinical centers. Double data entry will be performed at the Clinical Centers, utilizing the DMS tools available on the clients' workstations. The DCC will deploy a WORLD WIDE WEB based data management system for the implementation of the randomized clinical trial (RCT#1). A distributed rather than centralized DMS will be utilized for data submission. To achieve distribution of the DMS, a Web Browser (such as Netscape) must be available locally and, clinical site personnel will access the study database (DMS) via the WORLD WIDE WEB by connecting to the Web Server that resides at the DCC. The DCC Web Server will in turn connect with the DCC Database Server (this is a standard three tiered architecture configuration), which will provide secure access to the applications, and databases, which comprise the DMS.

There will be a manual back-up system for implementing randomization of participants in the event the DMS system is not functional at the time that randomization is required.

Validation checks will be performed at the centralized database to verify data accuracy and identify missing, unclear, illogical, or problematic responses. Queries will be generated to resolve discrepancies. Confidentiality will be strictly adhered to by assigning a unique participant identifier that will not identify the subject by name. The Manual of Procedures will define these processes in detail.

10 STATISTICAL CONSIDERATIONS

The proposed study design is a four-arm, double blind, RCT utilizing a 2×2 factorial design to evaluate the effect of oral ciprofloxacin (CIPRO®) and/or oral tamsulosin hydrochloride (FLOMAX®) in CP. An inactive placebo will be used for both ciprofloxacin (CIPRO®) and tamsulosin hydrochloride (FLOMAX®). The four treatment arms will be 1) placebo plus placebo, 2) ciprofloxacin (CIPRO®) plus placebo, 3) tamsulosin hydrochloride (FLOMAX®) plus placebo, 4) ciprofloxacin (CIPRO®) plus tamsulosin hydrochloride (FLOMAX®). A total of 184 participants will be enrolled. Details of the design considerations and statistical analysis, including sample size and power considerations, are described in the following sections. Additional details will be provided in the study Data Analysis and Monitoring Plan (DAMP), provided prior to study initiation.

10.1 Randomization and Stratification

To ensure balance across treatment groups within each clinical center, a stratified randomization approach will be used. Within each of the ten (10) clinical sites, subjects will be randomly allocated in equal proportions to the four treatment arms using a permuted block randomization procedure. In order to maintain blinding, each subject will be given a unique identifier number. The treatment code will be known only to the University of Pennsylvania Investigational Drug Service and the Data Coordinating Center Quality Assurance Manager until the completion of treatment and data collection on all participants.

10.2 Sample Size Calculations

The primary endpoint on which sample size estimates are based is the change in the overall NIH-CPSI score from baseline (randomization) to six (6) weeks. The total score has a potential range of 0 – 43 points. For each of the two primary comparisons--ciprofloxacin (CIPRO®) versus no ciprofloxacin (CIPRO®) or tamsulosin hydrochloride (FLOMAX®) versus no tamsulosin hydrochloride (FLOMAX®), we desire adequate numbers of participants to detect a difference of four (4) points in the change from baseline. We require 80% power to detect the specified difference between groups at a two-sided $\alpha = 0.05$ level of significance using a two-sample t-test. After adjustments to allow for possible dilution of statistical power due to interaction in the factorial design (50% increase), withdrawal (15% increase), clustering within Clinical Center (15% increase), a total of 184 participants or 184/4 = 46 participants per arm will be required. Total required sample sizes for alternative differences are shown in the table below.

Δ	**Trial Design**	**Total Sample Size using sd of change σ = 6.76**
3 points	2 arms 3 arms 4 arms 2 x 2	216 (108/arm) 420 (140/arm) 644 (61/arm) 324 (81/arm)
4 Points	2 arms 3 arms 4 arms 2 x 2	122 (61/arm) 237 (79/arm) 368 (92/arm) 184 (46/arm)
5 Points	2 arms 3 arms 4 arms 2 x 2	80 (40/arm) 156 (52/arm) 240 (60/arm) 120 (30/arm)

In addition, for each individual treatment arm of 46 subjects, the width of a 95% confidence interval for adverse event and other rates will be no wider than ± 15.0%. It is expected that these 184 participants can be accrued within approximately ten (10) months. Allowing for an additional twelve (12) weeks of follow-up on all participants, the entire study should require fourteen (14) months for completion.

10.3 Intent-to-Treat Analyses and Missing Data

An *intent-to-treat* analysis, for which all available data on all randomized participants are included, will be used for the primary comparison of treatments. All attempts will be made to keep missing data to a minimum and participants who withdraw from treatment will be encouraged to continue on study in order to provide complete follow-up information. However, it is expected that up to 15% of the randomized participants may withdraw prior to the final assessment of response at six (6) weeks. The loss of power due to withdrawals is incorporated into sample size calculation for the primary endpoint above. For secondary endpoints involving comparisons of response rates, these participants will be included in the denominator. The characteristics at time of randomization for those participants without complete follow-up will be examined; however, there will be limited statistical power to detect any but major differences between these participants and those with complete follow-up. In addition, in order to assess the potential biases introduced by differential withdrawal among treatment arms, a comparison of withdrawal rates and time to withdrawal will be included as an ancillary analysis to the primary endpoint comparison. Additional details of the evaluations of withdrawals are provided in the section regarding longitudinal data analysis below.

10.3.1 Data Safety Monitoring and Interim Analysis

Standard monitoring for adverse events and data quality will be performed on a regular basis. Details of frequency and content of monitoring will be outlined in the DAMP. These analyses will be presented to the External Advisory Committee.

Due to the expected rapid accrual and brief length of follow-up, no interim analysis comparing efficacy among groups will be conducted.

10.3.2 Statistical Analyses

In addition to the analyses described subsequently, descriptive statistics will be used during the course of the project as part of data management procedures for monitoring data quality. A brief overview of some of the statistical methods that may be used at the time of analysis, both for descriptive purposes and in more comprehensive analysis of the primary research questions, is summarized in the following sections. It is recognized that these methods may be revised, and additional ones considered, as the details of the specific analyses are developed. Details of the statistical analysis will be outlined in the Data Analysis and Monitoring Plan (DAMP).

Descriptive Analyses

Standard descriptive statistics will be used to describe baseline characteristics and follow-up measures, both overall and within each treatment group. Examination of baseline characteristics will include estimates of the distribution of age, race, and other demographic characteristics, baseline severity based upon pain/discomfort, urgency and frequency, and clinical center. These factors will be examined, both separately for each center, and combined across centers. Summary statistics such as means, medians, and ranges will be produced for all measured variables. Frequencies will be computed for all categorical and ordinal variables. Graphical methods including stem-and-leaf diagrams and boxplots will be used to examine distributions, identify potential influential points, and guide in the choice of transformations if warranted. The balance of baseline measures across the treatment groups will be compared using appropriate 2-sample and k-sample tests including analysis of variance (ANOVA), Wilcoxon and Kruskal-Wallis tests, and Fisher's exact tests.

Analysis of Primary Outcome

The analysis comparing the mean change in NIH-CPSI overall score from 0 to 6 weeks among treatment arms will utilize a linear regression model (equivalent to a 2-way analysis of variance) with a random effect to allow for clustering on clinical center. Standard regression diagnostics will be used to assess model adequacy and examine potential outlying or influential data points. Secondary analyses of the primary endpoint will include multivariable regression models to evaluate whether observed treatment differences, if any, can be partially accounted for by baseline differences in prognostic factors between treatment arms. Profiles of the overall NIH-CPSI score over time will also be compared among treatment groups using random effects regression models (35).

Secondary Analyses

A number of secondary analyses will be conducted, both to evaluate the secondary symptom-related outcomes and to supplement the primary endpoint comparison. Evaluation of some of the secondary outcomes will involve comparison of binary outcomes or response rates among groups. These endpoints may include the global assessment of change, change in white blood cell counts in the four-glass test, subscores of the NIH-CPSI, MOS SF12, and voiding frequency measured by a one day voiding log.

For example, one type of response will be defined based on the participant reported global assessment of chnage as measured at six (6) weeks or withdrawal, whichever comes first. A seven point scale will be used: 0) markedly worse; 1) moderately worse; 2) slightly worse; 3) no change; 4) slightly improved; 5) moderately improved; and 6) markedly improved. Participants who answer either 5) moderately or 6) markedly improved on this question will be considered to be responders. For this endpoint, participants who withdraw from the study for any reason (e.g. adverse events or participant choice) prior to six (6) weeks will be considered treatment non-responders. Following standard "intent-to-treat" methods, these withdrawals will be included in the denominator of the response rates for evaluation. This outcome will also serve as a validation for the primary endpoint above.

For binary outcomes, analyses comparing response rates will make use of the exact conditional test (ECT) version of Mantel-Haenszel methods to adjust for within-center clustering, as implemented within the Proc-StatXact software system(36). Additional analyses of such endpoints will rely on logistic regression and generalized estimating equation (GEE) methods to evaluate whether observed differences, if any, are attributable to imbalances in prognostic factors such as baseline symptom severity(37). The table below shows required sample sizes for comparison of response rates assuming 80% power to detect the specified difference between groups at a two-sided $\alpha = 0.05$ level of significance using the Fisher's exact test, with additional sample size adjustments as mentioned above. A baseline response rate of 30% is a typical placebo rate for symptom-related outcomes.

Smaller Response Rate	**Larger Response Rate**								
	30%	**35%**	**40%**	**45%**	**50%**	**55%**	**60%**	**65%**	**70%**
10%	288	204	152	116	96	80	68	56	48
20%	1248	600	364	248	176	140	108	88	72
30%		5648	1500	696	412	272	192	144	112
40%				6272	1620	740	428	276	192
50%						6396	1620	724	412

For the various measures evaluated over time, changes over time will be compared among treatment groups using methods for longitudinal data analysis(35). These methods will include random effects regression models for continuous outcomes and GEE methods for categorical and ordinal outcomes(35). Both within- and between-participant variability in these outcomes will be carefully assessed to provide pilot data for future clinical trials. For measures obtained only at baseline and one follow-up time point, change from baseline will be compared among groups using analysis of variance (ANOVA) and regression methods. When applicable, additional analyses of the symptom outcomes will include evaluation of time to response defined by specific changes in symptoms (e.g. 50% drop in symptom score). Associations between longitudinal changes in secondary outcomes and the overall participant assessment of improvement will be used to supplement the primary endpoint analysis and evaluate the validity of the symptom scales for assessing change.

Withdrawal rates will be compared among arms using standard methods for failure-time data including Kaplan-Meier curves, logrank tests, and Cox proportional hazards modeling(38). In addition, time to response will be compared among groups(38)

Post Treatment Period

Two sets of analyses will be done using post-treatment data (weeks 6-12). First, an analysis of the longitudinal changes in symptoms from 0 – 12 weeks will be done using the methods described above to evaluate durability of response. Secondly, an analysis of the time until need for rescue medication will be done using the survival methods described above. It is recognized that those participants who choose medications at the end of treatment will be considered failures at 6 weeks for this analysis.

10.3.3 Final Analysis

The final analysis of the data will take place after the completion of accrual, follow-up, and data collection and validation on all subjects. Details of the plans for final analysis will be outlined in the Data Analysis and Monitoring Plan (DAMP).

10.3.4 Statistical Computing

The appropriate ASCII and SAS data files will be extracted from the Oracle database for use in statistical analysis. Primary analyses, including graphical methods, will be implemented using various commercially available statistical packages including SAS(39),(40),(41),(42),(43),(44),(45),(46) and S-plus(47). The Proc StatXact for SAS Users software(36) will be used to compute the exact tests of discrete measures between groups. All software is currently available through the networked computing environment within the DCC.

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APPENDIX A

NIH-CPSI

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

		Yes	No
a.	Area between rectum and testicles (perineum)	❑1	❑0
b.	Testicles	❑1	❑0
c.	Tip of the penis (not related to urination)	❑1	❑0
d.	Below your waist, in your pubic or bladder area	❑1	❑0

2. In the last week, have you experienced:

		Yes	No
a.	Pain or burning during urination?	❑1	❑0
b.	Pain or discomfort during or after sexual climax (ejaculation)?	❑1	❑0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑0 Never
❑1 Rarely
❑2 Sometimes
❑3 Often
❑4 Usually
❑5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

❑0 Not at all
❑1 Less than 1 time in 5
❑2 Less than half the time
❑3 About half the time
❑4 More than half the time
❑5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑0 Not at all
❑1 Less than 1 time in 5
❑2 Less than half the time
❑3 About half the time
❑4 More than half the time
❑5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

8. How much did you think about your symptoms, over the last week?

❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑0 Delighted
❑1 Pleased
❑2 Mostly satisfied
❑3 Mixed (about equally satisfied and dissatisfied)
❑4 Mostly dissatisfied
❑5 Unhappy
❑6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c,1d, 2a, 2b, 3, and 4 = _____

Urinary Symptoms: Total of items 5 and 6 = _____

Quality of Life Impact: Total of items 7, 8, and 9 = _____

APPENDIX B

Consent Form

P.I. Name and Department
Telephone Numbers(s)
Co-P.I. Name(s)
Day Telephone Number(s)
24-Hour Emergency Number
IRB # of protocol

SUGGESTED PARTICIPANT CONSENT FORM

A MULTICENTER, RANDOMIZED CLINICAL TRIAL (RCT) TO EVALUATE THE EFFICACY OF ORAL CIPRO®, ORAL FLOMAX® AND THE COMBINATION OF ORAL CIPRO® & ORAL FLOMAX® FOR THE TREATMENT OF CHRONIC PROSTATITIS

Chronic Prostatitis Clinical Research Network (CPCRN)
CPCRN RCT#1 PROTOCOL

You are being asked to participate in a research study because you have been diagnosed with Chronic Prostatitis and have been informed that you may be eligible for the investigational study known as: "A Multicenter, Randomized Clinical Trial to Evaluate the Efficacy of Oral CIPRO®, Oral FLOMAX® and the Combination of Oral CIPRO® and Oral FLOMAX® for the Treatment of Chronic Prostatitis."

The CPCRN has been established by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) to identify and study treatments for people with symptoms of Chronic Prostatitis. It is hoped that such a study will eventually lead to improvement in the treatment of Chronic Prostatitis.

What is the purpose of the study?

The purpose of this study is to investigate the efficacy of ciprofloxacin (trade name: CIPRO®), a clinically available drug, and oral tamsulosin hydrochloride (trade name: Flomax®), to treat the symptoms of Chronic Prostatitis (CP). This study will attempt to determine if any of these treatments are effective in providing relief for CP: oral ciprofloxacin (CIPRO®), oral tamsulosin hydrochloride (FLOMAX®), or the combination of these two drugs.

An evaluation will be made to determine if you are eligible for this study. If so, and you agree to participate, you will be randomly assigned to one of four treatment groups. The combination of the medications you will receive in the study will be randomized, that is by chance, like a flip of a coin. Neither your physician nor you will know to which treatment group you will be assigned. Group One will receive two oral placebos (like sugar pills). Group Two will receive oral CIPRO® plus an oral placebo. Group Three will receive oral FLOMAX® plus an oral placebo. Group Four will receive oral CIPRO® plus oral FLOMAX®. However, information regarding which treatment you are receiving will be made available to your physician in case of an emergency.

What is Ciprofloxacin (CIPRO®)?

Ciprofloxacin has been approved by the United States Food and Drug Administration (FDA) for the treatment of infections in conditions such as: acute sinusitis (nasal sinus infection), lower respiratory tract infections (lower chest infection), urinary tract infections (bladder infection), chronic bacterial prostatitis (long term infection of the prostate gland), bone and joint infections, skin and intra-abdominal infections (infection within the part of the body between the chest and pelvis), infectious diarrhea, and typhoid fever. CIPRO® (and similar drugs) are often used to treat chronic prostatitis and you may have all ready been treated with this drug.

What is Tamsulosin Hydrochloride (FLOMAX®)?

Tamsulosin Hydrochloride (FLOMAX®) is an FDA approved drug for the treatment of the signs and symptoms of benign (non cancerous) prostatic hyperplasia (excessive, rapid reproduction of normal cells). FLOMAX® is a newer alpha-adrenergic agent (a substance that blocks transmission of stimuli) and is has been suggested that such drugs may be useful in the treatment of Chronic Prostatitis.

Who is being invited to participate in this study?

You will be invited to participate in this study if:

- You are a male;
- You must have had symptoms of discomfort or pain in the pelvic region for at least a three (3) month period within the last six (6) months;
- You have at least a moderate score on the National Institutes of Health (NIH)–Chronic Prostatitis Symptom Index (CPSI) with overall score ≥15 out of a potential of 0 - 43 points.

Approximately 184 participants with clinically diagnosed CP will be involved in this study. If you choose to participate, your involvement in the study will last at least 12 weeks.

What will I be asked to do if I participate in this study?

If you choose to participate in this study, and after you have signed and dated the consent form, the clinical research coordinator will evaluate your eligibility for the study. The following will then be performed:

1. Complete a through health history and physical examination.

The costs of these tests will be covered as part of the study. Your health history and physical examination will include 1) an abdominal examination, external genital exam, rectal exam, prostate exam, and perineal exam (area around the scrotum and anus), 2) urinalysis and a urine culture (examining a urine sample under a microscope to detect the presence of blood, infection and other processes, 3) an EPS specimen (expressed prostatic secretion) which involves a rectal exam. These tests will be repeated once at week six (6) during the twelve (12) week trial. You will also complete questionnaires to assess your pain/discomfort, Urinary Symptoms and a Quality of Life Index.

2. Take the study medication.

You need to take one or two tablets from each bottle of study medication once or twice a day. You will receive specific instructions regarding how to take the study medication by the research staff. You will take study medications for six (6) weeks.

3. Participate in study follow up.

You will be required to participate in 2 telephone contacts at week nine (9) and week twelve (12).

What benefits will I receive from the study?

You may receive no direct benefit from participating in this study. The purpose of this study is to determine the effectiveness of CIPRO®, FLOMAX® and the combination of CIPRO® and FLOMAX® to improve the symptoms of CP. Even though you may receive CIPRO® or FLOMAX®, or both, or a placebo, there is no assurance that you will receive any benefit from participating in this study. It is possible that your symptoms may even worsen while participating in this study. At the present time, no representation can be made that your participation will be of certain benefit.

What are the risks of participating in the study?

In general, oral administration of CIPRO® has been safe and well tolerated. CIPRO® may cause you to experience: nausea, vomiting, abdominal pain/discomfort, rash, agitation (nervousness), confusion, delirium, seizures or convulsions, dysphasia (difficulty speaking), constipation, dyspepsia (heartburn), flatulence (gas), hypersensivitiy to sunlight, hepatic necrosis (damage to the liver), jaundice (yellowing of the skin), pancreatitis (infection of the pancreas), colitis (inflammation of the colon), anemia (low blood count), prolongation of prothrombin time (lengthening of the time it takes for your blood to clot), elevation of certain elements in your blood (i.e. cholesterol, blood glucose, potassium), muscular pain, tendinitis/tendon rupture,

extremely rarely prolonged painful erection of the penis, worsening of the symptoms associated with hyperthyroidism (Graves Disease), allergic reaction, and taste loss.

For oral FLOMAX®, the side effects may include: headache, infection, dizziness, back and chest pain, skin rash, pruritis (itching), urticaria (development of raised itching skin areas), or angioedema (giant hives), sudden lowering of blood pressure, dizziness, fainting, lightheadedness, diarrhea, nausea, insomnia (difficulty sleeping), drowsiness, decreased libido and/or abnormal ejaculation, sinusitis (nasal infection), upper respiratory infection (infection in your upper airway), and visual disturbances.

What else do I need to know?

Alternatives

The alternative is not to participate in the study. Should you choose not to participate, you will receive the usual standard of medical care for your chronic prostatitis.

Voluntary Participation

Your participation in this study is voluntary. You are free to withdraw from the study at any time. If you decline to participate or choose to withdraw, you will still receive the same health care you would have otherwise received.

Confidentiality

You understand that every attempt will be made by the investigator to maintain all information collected in this study strictly confidential, except as required by law. You further understand that authorized representatives of the Sponsor, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), National Institute of Health (NIH), (insert your institution's name), as well as the Food and Drug Administration (FDA), will have access to and may copy, both your medical records and records from your participation in this study. This access is necessary to insure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this research, you will not be identified by name.

Financial Costs

You will not have to pay to be in this study.

Compensation

You will receive no money for enrolling in this study. CIPRO® and/or FLOMAX®, the study medications, will be provided free of charge during your participation.

Medical Treatment or Compensation for Injury

You understand that in the event of any physical injury resulting from the research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise available from the (**insert your Institution's name**).

New Information

If new information becomes available during the study that may impact on your willingness to continue to participate in the study, we will share that information with you.

Contact Persons

If at any time you have questions, concerns or comments about this study or a research-related injury, you should contact:

Telephone:
Principal Investigator:

Institutional Review Boards/Subject Rights

(Insert your Institution's name) has a committee called the Institutional Review Board (IRB). It is their responsibility to make sure that the research being conducted is safe and that people in the study are informed about risks and benefits of the research project. If you have questions regarding your rights as a research participant, or if problems arise which you do not feel you can discuss with Dr._____, please contact your doctor's IRB by calling **(Insert your IRB's name and phone number).**

PARTICIPANT'S STATEMENT:

I have read the above information about CIPRO® and FLOMAX® Study. I have been given an opportunity to ask questions about it and to discuss it with **Investigator's name or Authorized Personnel**. All of my questions/concerns have been answered to my satisfaction. I understand that I need to contact the (**insert your Institution's name and telephone number)**, if I move or change my telephone number. My signature below indicates my voluntary participation in this research program and that no procedures associated with this study have been performed on me prior to my signing this consent.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that I may refuse to participate or withdrawal from the study at any time without consequence to my present or future care at the (**insert your Institution's name)**.

DOCUMENTATION OF CONSENT

The original and one copy of this consent form will be kept in a research folder and a second copy of this Consent Form will be given to me to keep.

Consent of Subject:

I _____certify that I have explained to the subject named below the nature and purpose of the study, potential benefits, and possible risks associated with participation in the study. I have answered any questions that have been raised and have witnessed the signature of this subject. I have explained the information contained in this document to the subject on the date stated on this consent form.

_____	_____	_____
Name of Person Obtaining Consent (print)	**Signature**	**Date**

I have read and received a copy of this consent form. I agree voluntarily to participate in this research study.

_____	_____	_____
Name of Subject (print)	**Signature of Subject**	**Date**
_____	_____	_____
Legally Authorized Representative Signature (If Patient is Unable to Sign)	**Relationship to Patient**	**Date**
_____	_____	_____
Name of Investigator (print)	**Signature of Investigator**	**Date**
_____	_____	_____
Name of Impartial Witness (print)	**Signature of Witness**	**Date**

(Completed Only if patient or their legal representative is unable to read this consent form and an impartial witness is present for the entire discussion).

APPENDIX C

Study Visit Schedule

CPCRN Randomized Clinical Trial #1

FORMS ADMINISTRATION SCHEDULE

	Screening		+3 weeks	+6 weeks	+9 weeks	+12 weeks	Early Stop Treatment	Rescue Event
Form	Visit 1 *(clinic)*	Visit 2 *(clinic)*	Visit 3 *(phone)*	Visit 4 *(clinic)*	Visit 5 *(phone)*	Visit 6 *(phone)*	Visit 98 *(PRN)*	Visit 99 *(PRN)*
Eligibility Checklist (**ELIG**)	X							
NIH-CPSI (**CPSI**)	X	X	X	X	X	X	X	X
Randomization (RAND)		**X**						
SF-12 (**SF12**), Follow-Up Symptoms (**SYM**)		X	X	X	X	X	X	X
Demographics (**DEMO**)		X						
Dispensing Log (**DISP**)		X						
Concomitant Medication (**CMED**)		X		X				
Follow-Up Contacts (**FUP**)			X	X	X	X		
Adverse Events/Serious Adverse Events (**AE**)			X	X	X	X		
Medical History (**MED**)	X							
Physical Exam (**EXAM**)	X			X				
Four Glass Test Microscopy (**FGTM**)	X			X				
Four Glass Test Cultures (**FGTC**)	X			X				
Semen Sample (**SEMEN**)		X		X				
Uroflow and PVR (**URO**)		X		X*				
Voiding Log (**VOID**)		X		X				
Treatment Stop (**TSTOP**)				X			X	
Study Stop (**SSTOP**)						X		
Rescue Treatment Event (**RMED**)								X
Unmasking** (**UNMASK**)								
Patient Contact Information	X							
Visit Checklist	X	X	X	X	X	X	X	X
Study Medication Tracking Log		X		X				
Participant Status Log	X	X	X	X	X	X		
Participant ID Assignment Log	X							

* PVR Only.
** This form is completed only when clinically needed.

04032001 V2.1 Page 1 of 1 **SCHEDULE**

APPENDIX D

CIPRO®

Cipro Tablets (Bayer)

CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO® (ciprofloxacin) Oral Suspension are synthetic broad spectrum antimicrobial agents for oral administration. Ciprofloxacin hydrochlroide, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a weight of 385.8. empirical formula is $C_{17} H_{18} FN_3 O_3 \cdot HCl \cdot H_2 O$.

Ciprofloxacin is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17} H_{18} FN_3 O_3$ and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance.

Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

CIPRO® film-coated tablets are available in 100-mg, 250-mg, 500-mg and 750-mg (ciprofloxacin equivalent) strengths. The inactive ingredients are starch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, methylcellulose, titanium dioxide, polyethylene glycol and water.

Ciprofloxacin Oral Suspension is available in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g ciprofloxacin in 100 mL) strengths. Ciprofloxacin Oral Suspension is a white to slightly yellowish suspension with strawberry flavor which may contain yellow-orange droplets. It is composed of ciprofloxacin microcapsules and diluent which are mixed prior to dispensing (See instructions for USE/HANDLING). The components of the suspension have the following compositions:

Microcapsules--ciprofloxacin, polyvinylpyrrolidone, methacrylic acid copolymer, hydroxypropyl methylcellulose, magnesium stearate, and Polysorbate 20.

Diluent--medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.

CLINICAL PHARMACOLOGY

Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism.

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750-mg are 0.1, 0.2, and 0.4 µg/mL, respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000-mg.

A 500-mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750-mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg over 60 minutes every 8 hours. A 750-mg oral dose results in a C_{max} similar to that observed with a 400-mg I.V. dose. A 250-mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250-mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 mg/mL during the first two hours and are approximately 30 mg/mL at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

With oral administration, a 500-mg dose, given as 10 mL of the 5% CIPRO® Suspension (containing 250-mg ciprofloxacin/5 mL) is bioequivalent to the 500-mg tablet. A 10 mLvolume of the 5% CIPRO® Suspension (containing 250-mg ciprofloxacin/5mL) is bioequivalent to a 5 mL volume of the 10% CIPRO® Suspension (containing 500-mg ciprofloxacin/5mL).

When CIPRO® Tablet is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour whereas there is no delay observed when CIPRO® Suspension is given with food. The overall absorption of CIPRO® Tablet or CIPRO® Suspension, however, is not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension are also not affected by food. Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. (See **PRECAUTIONS**.)

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. **(See PRECAUTIONS.)**

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required. (See **DOSAGE AND ADMINISTRATION**.)

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs.

After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Microbiology Ciprofloxacin has in *vitro* activity against a wide range of gram-negative and gram- positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA. Ciprofloxacin does not cross- react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. *In vitro* studies have shown that additive activity often results when ciprofloxacin is combined with other antimicrobial agents such as beta-lactams, aminoglycosides, clindamycin, or metronidazole. Synergy has been reported particularly with the combination of ciprofloxacin and beta-lactam; antagonism is observed only rarely.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO® (ciprofloxacin) 5% and 10% Oral Suspension.

Aerobic gram-positive microorganisms

Enterococcus faecalis
(Many strains are only moderately susceptible.)

Staphylococcus aureus (methicillin susceptible)

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus pneumoniae

Streptococcus pyogenes

Aerobic gram-negative microorganisms

Campylobacter jejuni

Citrobacter diversus

Citrobacter freundii

Enterobacter cloaca

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Aerobic gram-negative microorganisms (Cont.)

Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella typhi
Serratia marcescens
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO® I.V. (ciprofloxacin for intravenous infusion).

Aerobic gram-positive microorganisms

Enterococcus faecalis

Many strains are only moderately susceptible.)

Staphylococcus aureus (methicillin susceptible)

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus pneumoniae

Streptococcus pyogenes

Aerobic gram-negative microorganisms

Citrobacter diversus

Citrobacter freundii

Aerobic gram- negative microorganisms (Cont.)

Enterobacter cloacae Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Morganella morganii

Proteus mirabilis

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas aeruginosa

Serratia marcescens

The following *in vitro* data are available, **but their clinical significance is unknown**.

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against most (>=90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram- positive microorganisms

Staphylococcus haemolyticus

Staphylococcus hominis

Aerobic gram-negative microorganisms

Acinetobacter Iwoffi

Aeromonas hydrophila

Edwardsiella tarda

Enterobacter aerogenes

Klebsiella oxytoca

Aerobic gram-negative microorganisms (cont.)

Legionella pneumophila

Pasteurella multocida

Salmonella enteritidis

Vibrio cholerae

Vibrio parahaemolyticus

Vibrio vulnificus

Yersinia enterocolitica

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro.* The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation).

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [1] (broth or agar) or < equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.
Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorgansims to ciprofloxacin.

The current absenceof data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures.

INDICATIONS AND USAGE

CIPRO® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute Sinusitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae,* or *Moraxella catarrhalis*.

Lower Respiratory Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

Urinary Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter clocae. Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis*.

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus.* (See **DOSAGE AND ADMINISTRATION**.)

Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis*.
Complicated Intra-Abdominal Infections (used in combination with metronidazole) caused by Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae, or Bacteroides fragilis. (See **DOSAGE AND ADMINISTRATION**.)

Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus* (methicillin susceptible), *Staphylococcus epidermidis,* or *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni, Shigella boydii* *, *Shigella dysenteriae, Shigella flexneri* or *Shigella sonnei* * when antibacterial therapy is indicated.

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi*.

NOTE: The efficacy of ciprofloxacin in the eradication of the chronictyphoid carrier state</A> has not been demonstrated.

Uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae*.

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*Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

If < anaerobic organisms are suspected of contributing to the infection, appropriate therapy</A> should be administered.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with CIPRO® may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

CIPRO® (ciprofloxacin hydrochloride) is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use Pregnancy,** and **Nursing Mothers** subsections.) The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone- class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy, renal dysfunction). (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS**.)

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse effects have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C. *difficile* colitis.

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after three months.

PRECAUTIONS

General: Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See **ANIMAL PHARMACOLOGY**). Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Quinolones, including ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See **WARNINGS, Information for Patients**, and **Drug Interactions**.)

Alteration of the dosage regimen is necessary for patients with impairment of renal function. (See **DOSAGE AND ADMINISTRATION**.)

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Information for Patients:

Patients should be advised:

- that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should be advised to drink fluids liberally and not take antacids containing magnesium, aluminum, or calcium, products containing iron or multivitamins containing zinc. Ciprofloxacin should not be taken concurrently with milk or yogurt alone, since absorption of ciprofloxacin may be significantly reduced. Dietary calcium as part of a meal, however, does not significantly affect ciprofloxacin absorption.
- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
- to avoid excessive sunlight or artificial ultraviolet light while receiving ciprofloxacin and to discontinue therapy if phototoxicity occurs.
- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain inflammation, or rupture of a tendon.
- that ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.
- that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking the drug if there is a history of this condition.

Drug Interactions: As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See **WARNINGS**.) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

Concurrent administration of ciprofloxacin with antacids containing magnesium, aluminum, or calcium; with sucralfate or divalent and trivalent cations such as iron may substantially interfere with the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired. To a lesser extent this effect is demonstrated with zinc-containing multivitamins. (See **DOSAGE AND ADMINISTRATION** for concurrent administration of these agents with ciprofloxacin.)

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated of the patient condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Carcinogenesis Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative)

E. *coli* DNA Repair Assay (Negative)

Mouse Lymphoma Cell Forward Mutation Assay (Positive)

Chinese Hamster V_{79} Cell HGPRT Test (Negative)

Syrian Hamster Embryo Cell Transformation Assay (Negative)

Saccharomyces cerevisiae Point Mutation Assay (Negative)

Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)

Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose upon mg/m ^{2}), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.[3]

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans in unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (0.8 times the highest recommended human dose of 1200 mg based upon body surface area) revealed no evidence of impairment.

Pregnancy: Teratogenic Effects. Pregnancy Category C: Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (See **WARNINGS**.)

Nursing Mothers: Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin I.V. 10 mg/kg/dose q8h for one week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and tobramycin I.V. 3 mg/kg/dose q8h for a total of 10-21 days. Patients less than 5 years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

In the study, injection site reactions were more common in the ciprofloxacin group (24%) than in the comparison group (8%). Other adverse events were similar in nature and frequency</A> between treatment arms. Musculoskeletal adverse events were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. One of sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities eight months after treatment. However, the relationship of this event to the patient' course of ciprofloxacin can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

ADVERSE REACTIONS

During clinical investigation with the tablet, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of patients treated, possibly related in 9.2% (total of 16.5% thought to be possibly or probably related to drug therapy), and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of patients treated, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin patients are listed below.

CARDIOVASCULAR palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

CENTRAL NERVOUS SYSTEM: dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesias (See above.) (See **PRECAUTIONS**.)

GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding (See above.) Cholestatic jaundice has been reported.

MUSCULOSKELETAL arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout.

RENAL UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism.

SKIN HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.)

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. (See **WARNINGS**.)

SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In domestic clinical trials involving 214 patients receiving a single 250-mg oral dose, approximately 5% of patients reported adverse experiences without reference to drug relationship. The most common adverse experiences were vaginitis (2%), headache (1%), and vaginal pruritus (1%). Additional reactions, occurring in 0.3%-1% of patients, were abdominal discomfort, lymphadenopathy, foot pain, dizziness, and breast pain. Less than 20% of these patients had laboratory values obtained, and these results were generally consistent with the pattern noted for multi-dose therapy.

In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets (500 mg BID) to cefuroxime axetil 250 mg - 500 mg BID) and to clarithromycin (500 mg BID) in patients with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse event profile comparable to the control drugs.

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship</A> to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:

BODY AS A WHOLE: change in serum phenytoin.

CARDIOVASCULAR postural hypotension, vasculitis.

CENTRAL NERVOUS SYSTEM: agitation, confusion, delirium, dysphasia, myoclonus, nystagmus, toxic psychosis.

GASTROINTESTINAL: constipation, dyspepsia, flatulence, hepatic necrosis, jaundice, pancreatitis, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.)

HEMIC LYMPHATIC: agranulocytosis, hemolytic anemia, methemoglobinemia, prolongation of prothrombin time.

METABOLIC/NUTRITIONAL: elevation of serum triglycerides, cholesterol, blood glucose, serum potassium.

MUSCULOSKELETAL: myalgia, possible exacerbation of myasthenia gravis, tendinitis tendon rupture.

RENAL/UROGENITAL: albuminuria, candiduria, renal calculi, vaginal candidiasis.

SKIN/HYPERSENSITIVITY: anaphylactic reactions, erythema multiforme/Stevens Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis.

SPECIAL SENSES: anosmia, taste loss (See **PRECAUTIONS**.)

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship are listed below:

Hepatic--Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic--Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal--Elevations of serum creatinine (1.1%), BUN (0.9%), CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, leukocytosis.

OVERDOSAGE

In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period at the highest oral doses tested; up to 5000 mg/kg in either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed included hypoactivity and cyanosis in both rodent species and severe vomiting in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin >2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.

DOSAGE AND ADMINISTRATION

The recommended adult dosage for acute sinusitis is 500-mg every 12 hours.

Lower respiratory tract infections may be treated with 500-mg every 12 hours. For more severe or complicated infections, a dosage of 750-mg may be given every 12 hours.

Severe/complicated urinary tract infections or urinary tract infections caused by organisms not highly susceptible to ciprofloxacin may be treated with 500-mg every 12 hours. For other mild/moderate urinary infections, the usual adult dosage is 250-mg every 12 hours.

In acute uncomplicated cystitis in females, the usual dosage is 100-mg every 12 hours. For acute uncomplicated cystitis in females, 3 days of treatment is recommended while 7 to 14 days is suggested for other mild/moderate, severe or complicated urinary tract infections.

The recommended adult dosage for chronic bacterial prostatitis is 500-mg every 12 hours.

The recommended adult dosage for oral sequential therapy of complicated intra-abdominal infections is 500-mg every 12 hours. (To provide appropriate anaerobic activity, metronidazole should be given according to product labeling.) (See CIPRO® I.V. package insert.)

Skin and skin structure infections and bone and joint infections may be treated with 500-mg every 12 hours. For more severe or complicated infections, a dosage of 750-mg may be given every 12 hours.

The recommended adult dosage for infectious diarrhea or typhoid fever is 500-mg every 12 hours. For the treatment of uncomplicated urethral and cervical gonococcal infections, a single 250-mg dose is recommended.

Complicated Intra-Abdominal Infections: Sequential therapy [parenteral to oral - 400-mg CIPRO® I.V. q 12 h (plus I.V. metronidazole) -> 500-mg CIPRO® Tablets q 12 h (plus oral metronidazole)] can be instituted at the discretion of the physician.

The determination of dosage for any particular patients must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient' host-defense mechanisms, and the status of renal function and hepatic function.

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Chronic Bacterial Prostatitis should be treated for 28 days. Infectious diarrhea may be treated for 5-7 days. Typhoid fever should be treated for 10 days.

Concurrent Use With Antacids or Multivalent Cations: Concurrent administration of ciprofloxacin with sucralfate or divalent or trivalent cations such as iron or antacids containing magnesium, aluminum, or calcium may substantially interfere with the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired. Therefore, concurrent administration of these agents with ciprofloxacin should be avoided. However, usual dietary intake of calcium has not been shown to alter the bioavailability of ciprofloxacin. Single dose bioavailability studies have shown that antacids may be administered either 2 hours after or 6 hours before ciprofloxacin dosing without a significant decrease in bioavailability. Histamine H_2 -receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Impaired Renal Function: Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction.

In patients with severe infections and severe renal impairment, a unit dose of 750-mg may be administered at the intervals noted above; however, patients should be carefully monitored and the serum ciprofloxacin concentration should be measured periodically. Peak concentrations (1-2 hours after dosing) should generally range from 2 to 4 μg/mL.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional guidance for adjusting dosage.

HOW SUPPLIED

CIPRO® (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-coated tablets containing 100-mg or 250-mg ciprofloxacin. The 100-mg tablet is coded with the word "CIPRO" on one side and "100" on the reverse side. The 250-mg tablet is coded with the word "CIPRO" on one side and "250" on the reverse side. CIPRO® is also available as capsule shaped, slightly yellowish film-coated tablets containing 500-mg or 750-mg ciprofloxacin. The 500-mg tablet is coded with the word "CIPRO" on one side and "500" on the reverse side. The 750-mg tablet is coded with the word "CIPRO" on one side and "750" on the reverse side. CIPRO® 250-mg, 500-mg, and 750-mg are available in bottles of 50, 100, and Unit Dose packages of 100. The 100-mg strength, is available only as CIPRO® Cystitis pack containing 6 tablets for use only in female patients with acute uncomplicated cystitis.

ANIMAL PHARMACOLOGY

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested (See **WARNINGS**.) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in beagles, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy has been noted after single oral doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration.

In dogs, ciprofloxacin at 3 and 10 mg/kg by rapid IV injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release, since they are partially antagonized by pyrilamine, an antihistamine. In rhesus> monkeys, rapid IV injection also produces hypotension but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of nonsteroidal anti-inflammatory drugs such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

CLINICAL STUDIES

Acute Sinusitis Studies

Ciprofloxacin tablets (500-mg BID) were evaluated for the treatment of acute sinusitis in two randomized, double-blind, controlled clinical trials conducted in the United States. Study 1 compared ciprofloxacin with cefuroxime axetil (250-mg BID) and enrolled 501 patients (400 of which were valid for the primary efficacy analysis). Study 2 compared ciprofloxacin with clarithromycin (500-mg BID) and enrolled 560 patients (418 of whom were valid for the primary efficacy analysis). The primary test of cure endpoint was a follow-up visit performed approximately 30 days after the completion of treatment with study medication.

In ciprofloxacin-treated patients enrolled in controlled and uncontrolled acute sinusitis studies, all of which included antral puncture, bacteriological eradication/presumed eradication was documented at the 30 day follow-up visit in 44 of 50 (88%) *H. influenzae*, 17 of 21 (80.9%) *M. catarrhalis*, and 42 of 51 (82.3%) *S. pneumoniae*. Patients infected with *S. pneumoniae* strains whose baseline susceptibilities were intermediate or resistant to ciprofloxacin had a lower success rate than patients infected with susceptible strains.

Uncomplicated Cystitis Studies

Efficacy: Two U.S. double-blind, controlled clinical studies of acute uncomplicated cystitis in women compared ciprofloxacin 100-mg BID for 3 days to ciprofloxacin 250-mg BID for 7 days or control drug.

APPENDIX E

FLOMAX®

Flomax Capsules (Boehringer Ingelheim)

DESCRIPTION

Tamsulosin hydrochloride is an antagonist of alpha $_{1A}$ adrenoceptors in the prostate.

Tamsulosin HCl is (-)-(*R*)-5-[2-[[2-(0-ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Tamsulosin HCl occurs as white crystals that melt with decomposition at approximately 230°C. It is sparingly soluble in water and in methanol, slightly soluble in glacial acetic acid and in ethanol, and practically insoluble in ether.

The empirical formula of tamsulosin HCl is C $_{20}$ H $_{28}$ N $_{2}$ O $_{5}$ S HCl. The molecular weight of tamsulosin HCl is 444.98.

Each FLOMAX capsule for oral administration contains tamsulosin HCl 0.4 mg, and the following inactive ingredients methacrylic acid copolymer, microcrystalline cellulose, triacetin, polysorbate 80, sodium laurylsulfate, calcium stearate, talc, FD&C blue No. 2, titanium dioxide, ferric oxide, gelatin, and trace amounts of shellac, industrial methylated 74OP, soya lecithin, 1-ethoxyethanol, dimethylpolysiloxane, and black iron oxide E172.

CLINICAL PHARMACOLOGY

The symptoms associated with hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of alpha$_1$ adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement urine flow rate and a reduction in symptoms of BPH.

Tamsulosin, an alpha$_1$ adrenoceptor blocking agent, exhibits selectivity for alpha$_1$ receptors in the human prostate. At least three discrete alpha$_1$ adrenoceptor subtypes have been identified: alpha$_{1A}$, alpha$_{1B}$ and alpha$_{1D}$; their distribution differs between human organs and tissue. Approximately 70% of the alpha$_1$ - receptors in human prostate are of the alpha$_{1A}$ subtype.

FLOMAX capsules are not intended for use as an antihypertensive drug.

Pharmacokinetics: The pharmacokinetics of tamsulosin HCl have been evaluated in adult healthy volunteers and patients with BPH after single and/or multiple administration with doses ranging from 0.1 mg to 1 mg.

Absorption: Absorption of tamsulosin HCl from FLOMAX capsules 0.4 mg is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin HCl exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.

Effect of Food: The time to maximum concentration (T_{max}) is reached by four to five hours under fasting conditions and by six to seven hours when FLOMAX capsules are administered with food. Taking FLOMAX capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (C_{max}) compared to fed conditions.

Distribution: The mean steady-state apparent volume of distribution of tamsulosin HCl after intravenous administration to ten healthy male adults was 16L, which is suggestive of distribution into extracellular fluids in the body. Additionally, whole body autoradiographic studies in mice and rats and tissue distribution in rats and dogs indicate that tamsulosin HCl is widely distributed to most tissues including kidney, prostate, liver, gall bladder, heart, aorta, and brown fat, and minimally distributed to the brain, spinal cord, and testes.

Tamsulosin HCl is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL). The results of two-way *in vitro* studies indicate that the binding of tamsulosin HCl to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin HCl had no effect on the extent of binding of these drugs.

Metabolism: There is no enantiometric bioconversion from tamsulosin HCl [R(-) isomer] to the S(+)isomer in humans. Tamsulosin HCl is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. Additionally, the cytochrome P450 enzymes that primarily catalyze the Phase I metabolism of tamsulosin HCl have not been conclusively identified. Therefore, possible interactions with other cytochrome P450 metabolized compounds cannot be discerned with current information. The metabolites of tamsulosin HCl undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin HCl and amitriptyline, albuterol (beta agonist), glyburide (glibenclamide) and finasteride (5alpha-reductase inhibitor treatment of BPH). However, results of the *in vitro* testing of the tamsulosin HCl interaction with diclofenac and warfarin were equivocal.

Excretion: On administration of the radiolabeled dose of tamsulosin HCl to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours.

Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin HCl in plasma range from five to seven hours. Because of absorption rate-controlled pharmacokinetics with FLOMAX capsules, the apparent half-life of tamsulosin HCl is approximately 9 to 13 hours in healthy volunteers and 14 to 15 hours in the target population. Tamsulosin HCl undergoes clearance in humans, with a relatively low systemic clearance (2.88 L[hairsp]/h).

Special Populations: Geriatrics (Age): Cross-study comparison of FLOMAX capsules overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin HCl may be slightly prolonged in geriatric males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin HCl binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Renal Dysfunction: The pharmacokinetics of tamsulosin HCl have been compared in 6 subjects with mild - moderate (30</=CLcr < 70 mL/min/1.73m^2) or moderate - severe (10 </=CLcr < 30 mL/min/1.73m^2) renal impairment and 6 normal subjects (CLcr < 90 mL/min/1.73m^2). While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin HCl, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in FLOMAX capsules dosing. However, patients with endstage renal disease (CLcr < 10 mL/min/1.73m^2) have not been studied.

Hepatic Dysfunction: The pharmacokinetics of tamsulosin HCl have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin HCl does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin HCl. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in FLOMAX capsules dosage.

Drug-Drug Interactions: Nifedipine, Atenolol, Enalapril: In three studies in hypertensive subjects (age range 47-79 years) whose blood pressure was controlled with stable doses of Procardia XL®, atenolol, or enalapril for at least three months, FLOMAX capsules 0.4 mg for seven days followed by FLOMAX capsules 0.8 mg for another seven days (n=8 per study) resulted in no clinically significant effects on blood pressure and pulse rate compared to placebo (n=4 per study). Therefore, dosage adjustments are not necessary when FLOMAX capsules are administered concomitantly with Procardia XL®, atenolol, or enalapril.

Warfarin: A definitive drug-drug interaction study between tamsulosin HCl and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules.

Digoxin and Theophylline: In two studies in healthy volunteers (n=10 per study; age range 19-39 years) receiving FLOMAX capsules 0.4 mg/day for two days, followed by FLOMAX capsules 0.8 mg/day for five to eight days, single intravenous doses of digoxin 0.5 mg or theophylline 5 mg/kg resulted in no change in the pharmacokinetics of digoxin or theophylline. Therefore, dosage adjustments are not necessary when a FLOMAX capsule is administered concomitantly with digoxin or theophylline.

Furosemide: The pharmacokinetic and pharmacodynamic interaction between FLOMAX capsules 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in ten healthy volunteers (age range 21-40 years). FLOMAX capsules had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11% to 12% reduction in tamsulosin HCl Cmax and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the FLOMAX capsules dosage.

Cimetidine: The effects of cimetidine at the highest recommended dose (400 mg every six hours for six days) on the pharmacokinetics of a single FLOMAX capsule 0.4 mg dose was investigated in ten healthy volunteers (age range 21-38 years. Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin HCl which resulted in a moderate increase in tamsulosin HCl AUC (44%). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Clinical Studies: Four placebo-controlled clinical studies and one active-controlled clinical study enrolled a total of 2296 patients (1003 received FLOMAX capsules 0.4 mg once daily, 491 received FLOMAX capsules 0.8 mg once daily, and 802 were control patients) in the U.S. and Europe.

In the two U.S. placebo-controlled, double-blind, 13-week, multicenter studies [Study 1 (US92-03A) and Study 2 (US93-01)], 1486 men with the signs and symptoms of BPH were enrolled. In both studies, patients were randomized to either placebo, FLOMAX capsules 0.4 mg once daily, or FLOMAX capsules 0.8 mg once daily. Patients in FLOMAX capsules 0.8-mg once daily treatment groups received a dose of 0.4 mg once daily for one week before increasing to the 0.8-mg once daily dose. The primary efficacy assessments included 1) total American Urological Association (AUA) Symptom Score questionnaire, which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms, where a decrease in score is consistent with improvement in symptoms; and 2) peak urine flow rate, where an increased peak urine flow rate value over baseline is consistent with decreased urinary obstruction.

Mean changes from baseline to week 13 in total AUA Score were significantly greater for groups treated with FLOMAX capsules 0.4 mg and 0.8 mg once daily compared to placebo in both U.S. studies. The changes from baseline to week 13 in flow rate were also significantly greater for the

FLOMAX capsules 0.4-mg and 0.8-mg once daily groups compared to placebo in Study 1, and for the FLOMAX capsules 0.8-mg once daily group in Study 2. Overall there were no significant differences in improvement observed in total AUA Symptom Scores or peak urine flow rates between the 0.4-mg and the 0.8-mg dose groups with the exception that the 0.8-mg dose Study 1 had a significantly greater improvement in total AUA Symptom Score compared to the 0.4-mg dose.

Mean total AUA Symptom Scores for both FLOMAX capsules 0.4-mg and 0.8-mg once daily groups showed a rapid decrease starting at one week after dosing and remained decreased through 13 weeks in both studies.

In Study 1, 400 patients (53% of the originally randomized group) elected to continue in their originally assigned treatment groups in a double- blind, placebo controlled, 40 week extension trial (138 patients on 0.4 mg, 135 patients on 0.8 mg and 127 patients on placebo). Three hundred and twenty-three patients (43% of the originally randomized group) completed one year. Of these, 81% (97 patients) on 0.4 mg, 74% (75 patients) on 0.8 mg and 56% (57 patients) on placebo had a response >/=25% above baseline in total AUA Symptom Score at one year.

INDICATIONS AND USAGE

FLOMAX® (tamsulosin HCl) capsules are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia(BPH). FLOMAX capsules are not indicated for the treatment of hypertension.

CONTRAINDICATIONS

FLOMAX capsules are contraindicated in patients known to be hypersensitive to tamsulosin HCl or any component of FLOMAX capsules.

WARNINGS

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in FLOMAX capsule treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents there is a potential risk of syncope (see ADVERSE REACTIONS).

Patients beginning treatment with FLOMAX capsules should be cautioned to avoid situations where injury could result should syncope occur.

PRECAUTIONS

General

1) *Carcinoma of the prostate:* Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Patients should be evaluated prior to the start of FLOMAX capsules therapy to rule out the presence carcinoma of the prostate.

2) *Drug-Drug Interactions:* The pharmacokineticand pharmacodynamic interactions between FLOMAX capsules and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and FLOMAX capsules should NOT be used in combination with other alpha- blocking agents.

The pharmacokinetic interaction between cimetidine and FLOMAX capsules was investigated. The results indicate significant changes in tamsulosin HCl clearance (26% decrease) and AUC (44% increase). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Results from limited *in vitro* and *in vivo* drug-drug interaction studies between tamsulosin HCl and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules.

(See also drug-drug interaction studies in CLINICAL PHARMACOLOGY Pharmacokinetics subsection.)

Information for Patients (see Patient Package Insert)

Patients should be told about the possible occurrence of symptoms related to hypotension such as dizziness when taking FLOMAX capsules, and they should be cautioned about driving, operating machinery or performing hazardous tasks.

Patients should be advised not to crush, chew or open the FLOMAX capsules.

Laboratory Tests

No laboratory test interactions with FLOMAX capsules are known. Treatment with FLOMAX capsules for up to 12 months had no significant effect on prostate-specific antigen (PSA).

Pregnancy Teratogenic Effects, Pregnancy Category B. Administration of tamsulosin HCl to pregnant female rats at dose levels up to 300 mg/kg/day (approximately 50 times the human therapeutic AUC exposure) revealed no evidence of harm to the fetus. Administration of tamsulosin HCl to pregnant rabbits at dose levels up to 50 mg/kg/day produced no evidence of fetal harm. FLOMAX capsules are not indicated for use in women.

Nursing Mothers FLOMAX capsules are not indicated for use in women.

Pediatric Use FLOMAX capsules are not indicated for use in pediatric populations.

Carcinogenesis, Mutagenesis, and Impairment of Fertility Rats administered doses up to 43 mg/kg/day in males and 52 mg/kg/day in females had no increases in tumor incidence with the exception of a modest increase in the frequency of mammary gland fibroadenomas in female rats receiving doses >/= 5.4 mg/kg ($P < 0.015$). The highest doses of tamsulosin HCl evaluated

in the rat carcinogenicity study produced systemic exposures (AUC) in rats 3 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

Mice were administered doses up to 127 mg/kg/day in males and 158 mg/kg/day in females. There were no significant tumor findings in male mice. Female mice treated for 2 years with the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the incidence of mammary gland fibroadenomas ($P < 0.0001$) and adenocarcinomas ($P < 0.0075$). The highest dose levels of tamsulosin HCl evaluated in the mice carcinogenicity study produced systemic exposures (AUC) in mice 8 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

The increased incidences of mammary gland neoplasms in female rats and mice were considered secondary to tamsulosin HCl-induced hyperprolactinemia. It is not known if FLOMAX capsules elevate prolactin in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is not known.

Tamsulosin HCl produced no evidence of mutagenic potential *in vitro* in the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in Chinese hamster ovary cells or human lymphocytes. There were no mutagenic effects in the *in vivo* sister chromatid exchange and mouse micronucleus assay.

Studies in rats revealed significantly reduced fertility in males dosed with single or multiple daily doses of 300 mg/kg/day of tamsulosin HCl (AUC exposure in rats about 50 times the human exposure with the maximum therapeutic dose). The mechanism of decreased fertility in male rats is considered to be an effect of the compound on the vaginal plug formation possibly due to changes of semen content or impairment of ejaculation. The effects on fertility were reversible showing improvement by 3 days after a single dose and 4 weeks after multiple dosing. Effects on fertility in males were completely reversed within nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day tamsulosin HCl (1/5 and 16 times the anticipated human AUC exposure) did not significantly alter fertility in male rats. Effects of tamsulosin HCl on sperm counts or sperm function have not been evaluated.

Studies in females rats revealed significant reductions in fertility after single or multiple dosing with 300 mg/kg/day of the R-isomer or racemic mixture of tamsulosin HCl, respectively. In female rats, the reductions in fertility after single doses were considered to be associated with impairments in fertilization. Multiple dosing with 10 or 100 mg/kg/day of the racemic mixture did not significantly alter fertility in female rats.

ADVERSE REACTIONS

The incidence of treatment-emergent adverse events has been ascertained from six short-term U.S. and European placebo-controlled clinical trials in which daily doses of 0.1 to 0.8 mg FLOMAX capsules were used. These studies evaluated safety in 1783 patients treated with FLOMAX capsules and 798 patients administered placebo.

Signs and Symptoms of Orthostasis In the two U.S. studies, symptomatic postural hypotension was reported by 0.2% of patients (1 of 502) in the 0.4-mg group, 0.4% of patients (2 of 492) in the 0.8-mg group, and by no patients in the placebo group. Syncope was reported by 0.2% of patients (1 of 502) in the 0.4-mg group, 0.4% of patients (2 of 492) in the 0.8-mg group and 0.6% of patients (3 of 493) in the placebo group. Dizziness was reported by 15% of patients (75 of 502) in the 0.4-mg group, 17% of patients (84 of 492) in the 0.8-mg group, and 10% of patients (50 of 493) in the placebo group. Vertigo was reported by 0.6% of patients (3 of 502) in the 0.4-mg group, 1% of patients (5 of 492) in the 0.8 mg group and by 0.6% of patients (3 of 493) in the placebo group.

Multiple testing for orthostatichypotension was conducted in a number of studies. Such a test was considered positive if it met one or more of the following criteria: (1) a decrease in systolic blood pressure of >/=20 mmHg upon standing from supine position during the orthostatic tests; (2) a decrease in diastolic pressure >/=10 mmHg upon standing, with the standing diastolic blood pressure <65 mmHg during the test; (3) increase rate of >/=20 bpm upon standing with a standing pulse rate >/=100 bpm during test; and (4) the presence of clinical symptoms (faintness, lightheadedness/lightheaded, dizziness, spinning sensation, vertigo, or postural hypotension) upon standing during the orthostatic test.

Following the first dose of double-blind medication in Study 1, a positive orthostatic test result at 4 hours post-dose was observed in 7% of patients (37 of 498) who received FLOMAX capsules 0.4 mg once daily and in 3% of the patients (8 of 253) who received placebo. At 8 hours post-dose, a positive orthostatic test result was observed for 6% of the patients (31 of 498) who received FLOMAX capsules 0.4 mg once daily and 4% (9 of 250) who received placebo. (Note: patients in the 0.8-mg group received 0.4 mg once daily for the first week of Study 1.)

In Studies 1 and 2, at least one positive orthostatic test result was observed during the course of these studies for 81 of the 502 patients (16%) in the FLOMAX capsules 0.4-mg once daily group, 92 of the 491 patients (19%) in the FLOMAX capsules 0.8-mg once daily group and 54 of the 493 patients (11%) in the placebo group.

Because orthostasis was detected more frequently in FLOMAX capsule-treated patients than in placebo recipients, there is a potential risk of syncope (WARNINGS).

Abnormal Ejaculation Abnormal ejaculation ejaculation failure, disorder, retrograde ejaculation and ejaculation decrease. Withdrawal from these clinical studies of FLOMAX capsules because of abnormal ejaculation was also dose-dependent with 8 of 492 patients (1.6%) in the 0.8-mg group, and no patients in the 0.4-mg placebo groups discontinuing treatment due to abnormal ejaculation.

Post-Marketing Experience Allergic-type reactions such as skin rash angioedema tongue, lips and face and urticaria have been reported positive rechallenge in some cases.

OVERDOSAGE

Should overdosage of FLOMAX capsules lead to hypotension (See WARNINGS and ADVERSE REACTIONS), support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should then be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin HCl is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit.

One patient reported an overdose of thirty 0.4-mg FLOMAX capsules. Following the ingestion of the capsules, the patient reported a severe headache.

DOSAGE AND ADMINISTRATION: FLOMAX capsules 0.4 mg once daily is recommended as the dose for the treatment of the signs and symptoms of BPH. It should be administered approximately one-half hour following the same meal each day.

For those patients who fail to respond to the 0.4-mg dose after two to four weeks of dosing, the dose of FLOMAX capsules can be increased to 0.8 mg once daily. If FLOMAX capsules administration is discontinued or interrupted for several days at either the 0.4-mg or 0.8-mg dose, therapy should be started again with the 0.4-mg once daily dose.

HOW SUPPLIED: FLOMAX capsules 0.4 mg are supplied in density polyethylene bottles containing 100 or 1000 hard gelatin capsules with green opaque cap and orange opaque body. The capsules are imprinted on one side with "Flomax 0.4 mg" and on the other side with "BI 58."

APPENDIX F

Lab Procedures

Four Glass Test - Procedure

Participant Test Schedule: (Screening Visit #1): 4 glass urine microscopy and culture

(Visit #4 - Week 6): 4 glass urine microscopy and culture

1. Instruct participant to retract foreskin (if uncircumcised).
2. Wipe head of penis with one alcohol pad.
3. Collect the first 10 ml sample **(VB1)** directly into sterile container. (Range 5 - 30 ml)
   Centrifuge, examine and culture as described below.*****
4. Collect midstream sample **(VB2)**.
   Dip VB2 for pH, glucose and protein. Record results
   Centrifuge, examine and culture as described below.*****
5. **EPS** - Prostatic massage
   a.) Collect EPS on a sterile surface. (Example: lid of urine cup)
   b.) Estimate volume of EPS in µL. (1 drop ~ 50 µL)
   c.) Examine 5 µL at 400X power.
   Count WBC's, RBC's, hyphae.
   d.) Place 10 µL on sheep blood agar (5%) of a urocult paddle and incubate at 37°C for 5 days. Record results at 48 hours and five days.
   e.) If it grows, replate colonies on MacConkey agar for identification.
   f.) Store any remaining volume of EPS in 1.0 - 1.5 ml cryovials.
   g.) Snap freeze in liquid Nitrogen for later storage at -70°C.

6. Collect first 10 ml sample post massage **(VB3)** within 30 minutes. (Range 5 - 30 ml)
   Centrifuge, examine and culture as described below.*****

*** VB1, VB2 and VB3 SPECIMENS**

a.) Centrifuge 2-3 mls of urine for five minutes.
b.) Examine at 400X power.
c.) Count WBC's, RBC's, hyphae (average of three fields rounded to nearest whole number.)
d.) Place 100 µL of specimen on sheep blood agar (5%) plate and 100 µL of specimen on MacConkey agar plate.
e.) Culture at 37°C for 5 days. Record results at 48 hours and five days.

* **Chlamydia trachomatis PCR**

a.) Participant must not have urinated in the previous two (2) hours.
b.) Collect 10 to 50 mL of first catch urine into a clean, empty plastic cup without preservatives.
c.) Cap the specimen cup and label appropriately.
d.) The following is a list of molecular tests to be used:
- Geneprobe LCR
- Abbott LcX,
- Roche PCR (Cobas)
- Becton-Dickinson

Uroflow and Post Void Residual Procedure

Participant Test Schedule: (Screening Visit #2)
(Visit #4 – Week 6- **PVR ONLY**)

1. Instruct participant to have a full bladder for this test. A minimum volume of 150 cc's constitutes a valid test. This can be assessed by ultrasound of the bladder.
2. Record three values - Total Volume (ml)
Peak Flow (ml/second)
Mean Flow (ml/second)

Semen Sample Procedure

Participant Test Schedule: (Screening Visit #2)
(Post Clinic Visit #4*****)

1. Instruct participant to remain abstinent for a minimum of two days.
2. Collect specimen in a sterile urine cup.
3. Measure volume in mls.
4. Plate 100 µL on sheep blood agar (5%) plate and 100 µL on MacConkey agar. Culture at 37°C for 5 days. Record results at 48 hours and 5 days.
5. Allow sample to stand at room temperature for thirty minutes.
6. Centrifuge for five minutes.
7. Aliquot seminal plasma into 1.0 - 1.5 ml cryovials.

Peroxidase Staining Procedure:

Prepare Benzidine-Cyanosine stock solution:
1. Dissolve 62 mg Benzidine (Sigma cat. # B3383) in 24 ml Methanol using a 100ml-graduated cylinder.
(Have 200ml of deionized H_20 boiling in a beaker. Dip 100ml graduated cylinder into boiling water, 30 seconds at a time, until benzidine is dissolved)
2. Add 75 mg Cyanosine (Phloxine B, Sigma cat. #P2759).
3. Add 26 ml boiling deionized or triple distilled H_20.
4. Filter using Whatman #4 paper filter.

5. Store in brown bottle (solution is light sensitive) at room temperature for no more than 1 year.

Immediately prior to counting sample, make Benzidine-Cyanosine working solution:
1. Combine 1 ml Benzidine-Cyanosine stock solution (swirl vigorously before using) and 4 ul 3% H_2O_2.
2. Mix semen and Benzidine-Cyanosine working solution in 1:1 ratio (typically 20 ul each).
3. Place 20 ul of combination on a hemacytometer or slide with cover slip.
4. Scan slide under microscope at low power to assure even distribution of cells.
5. Count number of WBC per 5 high power fields (400X) after 5 minutes. WBC will be stained (pink/red) brown. Round cells which are not WBC (immature spermatids) will not be stained brown. The background will be pink.

***** Only for participants with localizing uropathogens at baseline visit #2 will provide semen sample 2-3 days after clinic visit #4.

APPENDIX G

Brochure

The CPCRN is comprised of the following ten clinical research centers and a Data Coordinating Center (DCC) which coordinates all activities related to the study.

PARTICIPATING CLINICAL CENTERS AND PRINCIPAL INVESTIGATORS

Brigham and Women's Hospital
Boston, MA
Michael P. O'Leary, MD, MPH

Cleveland Clinic Florida
Ft. Lauderdale, FL
Daniel Shoskes, MD

MLK Drew Medical Center
Los Angeles, CA
Nand S. Datta, MD

Northwestern University
Chicago, IL
Anthony J. Schaeffer, MD

Queen's University
Kingston, Ontario
J. Curtis Nickel, MD

Temple University
Philadelphia, PA
Michel A. Pontari, MD

University of Arizona
Tucson, AZ
Craig Comiter, MD

University of California – Los Angeles
Los Angeles, CA
Mark S. Litwin, MD, MPH

University of Maryland
Baltimore, MD
Richard B. Alexander, MD

University of Mississippi
Jackson, MS
Jackson E. Fowler, MD

University of Pennsylvania (DCC)
Philadelphia, PA
J. Richard Landis, PhD

For more information, please contact the medical center at the bottom of the page or Lee Randall, Project Manager, University of Pennsylvania
(215) 573-6318 Phone
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TO MAKE AN APPOINTMENT, PLEASE CONTACT:

CHRONIC PROSTATITIS COLLABORATIVE RESEARCH NETWORK (CPCRN)

RANDOMIZED CLINICAL TRIAL #1

INFORMATION FOR PATIENTS

CPCRN

Chronic Prostatitis (CP) is a disabling condition affecting an untold number of men of all ages and ethnic origins. CP is a disease of chronic pelvic discomfort and/or pain for which there is no standardized method of diagnosis and treatment. Under the direction of the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) and the National Institutes of Health (NIH), the Chronic Prostatitis Collaborative Research Network (CPCRN) has been established to study all aspects of this puzzling disease.

Men who have experienced pelvic discomfort and/or pain for at least three months and meet certain eligibility requirements, may be eligible to enroll in the first randomized clinical trial. Patients will be asked to comply with the following trial requirements:

- Symptom Questions
- Medical History
- Physical Exam
- Urine Specimen
- Semen Specimen
- Expressed Prostatic Secretions Specimen
- Uroflow Study
- Urethral Swab
- Voiding Log

Each procedure and questionnaire contributes a wealth of information to the trial database, which tracks information about *all* patients enrolled in the trial.

Confidentiality is guaranteed through the use of unique identification numbers for all patient information.

Once a patient is enrolled into the trial, he will be randomized into one of four treatment groups. This means you have a 75% chance of receiving a study drug. Patients will take the study drug or its matching placebo for 6 weeks and participate in a follow up period for an additional 6 weeks, for a total of 12 weeks. This study includes 3 doctor visits and 3 telephone contacts.

These established research steps will enable the CPCRN to study the natural history of this disease while testing diagnostic tools and potential therapies, with the ultimate goal to develop effective treatment for patients.

APPENDIX H

Chronic Prostatitis Collaborative Research Network RCT#1

Recruitment Video

I am Dr. Richard Alexander of the University of Maryland School of Medicine. I am one of the Principal Investigators in the Chronic Prostatitis Collaborative Research Network (abbreviated CPCRN), a group of 10 clinical centers and one data coordinating center in the U.S. and Canada studying Chronic Prostatitis or Chronic Pelvic Pain Syndrome. The institutions participating in the CPCRN are:

- Brigham and Women's Hospital, Boston, MA
- Cleveland Clinic Florida, Fort Lauderdale, FL
- MLK Drew Medical Center, Los Angeles, CA
- Northwestern University, Chicago, IL
- Queen's University, Kingston, Ontario, Canada
- Temple University, Philadelphia, PA
- University of Arizona, Tuscon, AZ
- University of California Los Angeles, Los Angeles, CA
- University of Maryland, Baltimore, MD
- University of Mississippi, Jackson, MS
- University of Pennsylvania, Philadelphia, PA (Data Coordinating Center)

First let me say that I am sorry that you have this problem. As you are probably aware, we know very little about chronic prostatitis and there is little objective information to guide us in your treatment. The CPCRN represents the first initiative of the National Institutes of Health, through the National Institute of Diabetes and Digestive and Kidney Diseases, to try and increase our understanding of chronic prostatitis. The first efforts of the CPCRN have been directed to simply try and understand what chronic prostatitis is to patients by recording the features of the disease over time in nearly 400 patients. The lack of information about the diagnosis, cause and treatment of chronic prostatitis is astonishing given how common the problem is. There are 2 million office visits annually in the U.S. for chronic prostatitis, making this among the most common diseases of the prostate.

I regret that we do not have good answers for the treatment of chronic prostatitis. It is precisely for this reason that we need your help. You have been asked to watch this brief video because you are a candidate for the first study of the **treatment** of chronic prostatitis that we in the CPCRN have organized. I would like to ask for your participation in the study as a patient.

We are performing a test of two drugs for the treatment of chronic prostatitis. These drugs, ciprofloxacin or Cipro and tamsulosin or Flomax, are representative of the most commonly used medical treatments for chronic prostatitis in the U.S. As hard as it is to believe, no controlled

studies of these drugs have ever been done to determine if they are safe and effective for the treatment of chronic prostatitis. Our study will directly answer this question. The study will compare each of these drugs individually, a combination of the two drugs together or a placebo, meaning no active drug. If you agree to participate, you will be randomly assigned to one of these treatment groups. You will not know which treatment you are getting and neither will the doctor who is taking care of you during the study.

You will take the study drug to which you are randomly assigned for six weeks. You will be followed in the office to see if the study drug changes your symptoms as assessed by several questionnaires that you will fill out at each visit. At the end of the study, we will have enough information to determine if any of the drug treatments results in a significant improvement in symptoms compared to the placebo group.

Patients often say to me when they see me in the office that they did not come to see me to be in a study, they came to get a cure. They want answers to this problem and I must say I do as well. But as I have to tell my patients with chronic prostatitis, there are no answers to this problem, and even the most commonly used therapies for it are not only unproven, they are untested.

It is easy to say we need answers, but it is very hard to actually get them. We are completely dependent upon the generosity of patients such as yourself who volunteer themselves to help us by participating in clinical studies. There is no other way to do this. There is only one way to get the answers that you and I want, and that is to ask a question, design an experiment and carry it out. That is precisely what we will do. Let me absolutely assure you that this is a very serious effort, with many talented individuals from North America contributing and coordinating their efforts to get this study completed properly.

You may ask "Why should I, as part of a study, take a drug that I have previously taken and that did not help me?" This is an excellent question and the answer is very important for you to understand. The answer is that if the drug really does not work, we must **know** this and must prove it in a population of men larger than just one. If the drugs do not work better than placebo, then we will establish that the standard therapy used to treat this disease in millions of men in this country is ineffective. This would strongly convince the scientific and health care community that new research and studies of chronic prostatitis are desperately needed. If the drugs do have some evidence of working in this disease, then this is also a very important fact to clearly establish as this will then serve as a proven therapy to which newer treatments can be compared. So, as you can see, no matter what the answer is to this question, it will be important.

This tape is not a substitute for a thorough discussion with your physician about the study, including the risks and benefits of your participation. Your participation is totally voluntary and you can withdraw from the study at any time if you desire to do so.

Finally, let me also tell you that if my father or one of my brothers had chronic prostatitis, I would encourage him to the best of my ability to enroll in this study. We need your help. I urge you in the strongest possible way to participate in this study. Thank you.

PROTOCOL AMENDMENT SIGNATURE PAGE

CHRONIC PROSTATITIS RESEARCH NETWORK (CPCRN)

Proposed Randomized Clinical Trial (RCT) #1

A MULTICENTER, RANDOMIZED CLINICAL TRIAL (RCT) TO EVALUATE THE EFFICACY OF ORAL CIPRO®, ORAL FLOMAX® AND THE COMBINATION OF ORAL CIPRO® & ORAL FLOMAX® FOR THE TREATMENT OF CHRONIC PROSTATITIS (CP)/CHRONIC PELVIC PAIN SYNDROME (CPPS)

Protocol Amendment #1 Version Date: November 26, 2001

As the Principal Investigator at _____site, I have read the above protocol amendment and I agree, that upon IRB approval, I will implement and comply with this amendment. Furthermore, I agree to oversee the compliance of my site staff (and subinvestigators, if applicable).

_____	_____	_____
PI's Signature	PI's Printed Name	Date

*Once signed, this original shall be maintained in the site's CPCRN RCT#1 Regulatory Binder and a copy should be faxed to the Project Manager at the DCC.