TAP HOLDINGS INC.

UPRIMA™ (APOMORPHINE HCL TABLETS) SUBLINGUAL

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1.0 Erectile Dysfunction

In 1993, the National Institutes of Health (NIH) Consensus Conference on Impotence altered the term impotence to the less pejorative term erectile dysfunction (ED). The NIH defined ED as the consistent inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance.[1] ED is a condition with profound psychosocial consequences affecting relationships and interfering with a man's self-esteem and confidence.[2]

Epidemiology

In 1989, ED was estimated to account for only 400,000 medical outpatient visits and 30,000 hospital admissions.[3] Over the past decade there has been a major alteration in the scientific and social understanding of this condition. The level of physician and patient education, as well as the public awareness of this condition has broadened. This, in addition to the introduction of the first oral agent, sildenafil citrate, has encouraged more men to seek medical assistance.

Although no data exist to document current clinic or hospital visits for ED, clinical practice indicates that the number of patients presenting for evaluation of this condition far exceeds that of 11 years ago. Despite this increase, the number of men with ED is still greater than the number of men who seek medical treatment.

There are a variety of reasons why patients are still reluctant to seek treatment; these include embarrassment, fear, and the lack of a partner.[4] Until recently, the lack of acceptable therapies has also been a significant deterrent to men seeking help. With the introduction of the first oral agent some of these barriers have lessened but there still remains an untreated population of men with ED.

ED has many etiologies and there are many patient and partner personal needs to consider in treatment. No one treatment is appropriate for all men. While many patients will be successfully treated with sildenafil, there are those who will fail to respond with

sufficient rigidity, those for whom it is medically inappropriate or contraindicated and others who cannot tolerate the medication. Thus, it is important to develop new noninvasive treatment choices for ED management as this new therapeutic area matures.

Sexual activity has been evaluated in a number of studies in the United States. However, defining the true incidence of ED has been hampered historically by poor epidemiological methodology. The two major methodological problems have been the use of non-representative patient sampling and the use of non-validated instruments. It was not until 1991, with the publication of the Massachusetts Male Aging Study (MMAS), that reliable epidemiological information became available.[5] This information has been supported by the US National Health and Social Life Survey (NHSLS) from which a selection of data related to ED were published in 1999.[6]

The MMAS was a cross-sectional, community-based, multidisciplinary epidemiological survey of aging and health in a random sample of men aged 40-70 years.[5] Conducted between 1987-1989 in the Boston area, it evaluated almost 1300 subjects using a detailed questionnaire. Nine of the 23 questions were relevant to achieving measures of erectile function. The study design allowed identification of statistically predictive factors. Four grades of self-rated impotence were used: normal, minimal, moderate and complete. In this analysis, the overall rate of ED was 52% (17% minimal, 25% moderate and 10% complete). The probability of complete ED increased from 5% to 15% from age 40 to 70 and the probability of any ED increased from 40% to 67% over the same age range. ED was positively correlated with increasing age, as well as health status and emotional function. From these data, it was estimated that there were 30 million men in the United States with ED.[1]

The NHSLS, conducted in 1992, was a study of sexual behavior in men and women.[6] A demographically representative cohort of 1410 men between the ages of 18-59 was analyzed. The authors believe that the cohort studied accounts for 97% of the population in the age range studied, approximating 150 million Americans. One of the primary outcome measures of this study was the risk of experiencing sexual dysfunction. The

questionnaire assessed seven variables in men: desire for sex, erectile function, orgasmic dysfunction, anxiety about sexual performance, premature ejaculation, pain during intercourse and pleasure associated with sex. In contrast to the MMAS, ED occurred in only 10% of the men studied. ED rates increased with increasing age; ED was three times more likely in men aged 50-59 years compared to men aged 18-29 years. ED was also correlated with poor health, and emotional and stress-related disorders.

The differences observed between the MMAS and NHSLS data may be related to differences in the age groups studied and differences in the instruments used. However, overall, the data derived from these two analyses indicate that ED is a prevalent problem and represents a significant public health concern.

Etiology

The causes of ED can be separated into two broad categories: organic (physiological) and psychogenic (psychological). Until recently, the majority of patients who presented with ED were considered to have psychogenic disorders. Current understanding of erectile pathophysiology, however, points to the existence of an organic component in most ED cases, with the frequency of organic etiology being much greater in older men.[7]

The distribution of etiologies of ED varies depending on the type of clinician questioned. Most urologists contend that the majority of ED is organic, whereas sex therapists contend that at least half of the patients they see have psychologically mediated ED.[8] It is likely that both are correct, in part because both conditions co-exist and because the patients are self-selected or pre-selected by referring physicians.

The diagnosis of ED is complicated because many patients present with more than one cause (often a mixture of organic and psychogenic etiologies). In 1990, Junemann categorized the etiologies of ED as vasculogenic, endocrinopathic, pharmacologic, iatrogenic, neurogenic and psychogenic.[9] These categories have been recognized by the nomenclature committee of the International Society for Impotence Research (ISIR).

It is generally accepted that the most common cause of ED is vascular pathology. The association between vascular disease processes and ED is well documented in the literature. The most common risk factors for this pathology include atherosclerosis, hypertension, diabetes, hypercholesterolemia and cigarette smoking.[2] In the MMAS analysis, vascular disease is clearly associated with ED.[5] Myocardial infarction and coronary artery bypass surgery are associated with ED in 64%[10] and 57%[11] of patients respectively. The incidence of ED in men with peripheral vascular disease is 80%.[12] ED occurs in approximately 10% of patients with untreated hypertension.[13] The prevalence of ED in diabetics ranges from 35-75%[2] and is related to the age of the patient as well as the nature of the disease, with Type I diabetics having a higher rate of ED. Fifty percent (50%) of diabetic men will develop ED within 5-10 years of their diagnosis of diabetes.[14]

Approximately 10-25% of all organic ED can occur as a result of medications prescribed for patients.[15] The most commonly implicated medications include anti-hypertensives, cardiac medications, psychotropics (including antidepressants), and anti-androgens. Certain surgical procedures (radical pelvic surgery such as radical prostatectomy and radical rectal surgery) are often associated with ED.[16]

Neurologic diseases that are associated with ED include cerebrovascular disease, brain tumors, Parkinson's disease, Alzheimer's disease, lumbar disc disease and multiple sclerosis (MS). Eighty-five (85%) of stroke patients and 70% of MS patients suffer from ED.[17,18] Neurogenic disease accounts for approximately 5% of all organic ED.

Primary psychogenic ED occurs under a wide variety of social and psychological circumstances, including depression. There are a number of well-recognized precipitants of psychogenic ED, including relationship deterioration, divorce, spousal death or illness, financial and career issues.[19]

Treatment Options

Pharmaceutical therapy for ED is somewhat different from the treatment of other diseases in men. The disease is not life-threatening, and although it is usually partly physical in origin, it can have significant psychogenic consequences for both patient and partner. The treatment of ED is elective, and the patient will suffer no obvious physical sequelae as a result of discontinuing therapy. Sexual activity is, by its nature, intermittent, and it generally involves a partner whose support is integral to successful treatment. Both patient and partner must be sufficiently motivated to begin a therapy which may involve a period of frustration as technique, timing and dosing are mastered. These frustrations may result in a relatively higher rate of discontinuation among ED patients compared to patients receiving treatment for other diseases.

Summary

In summary, ED is a prevalent problem related to patient age and health status. As the male population ages, the number of men with this condition will continue to increase. ED is caused by a variety of medical and psychological conditions. It has a profound impact upon the psychosocial well being of the patient as well as his partner. While effective treatment exists that can be used universally, such as prosthesis placement, most men find such treatment unacceptable. Intracavernous injection and transurethral treatments are also effective, but also unacceptable to many patients. Sildenafil, a non-invasive therapy, is not appropriate for all patient populations since safety concerns and lack of efficacy in some patients limit its utility. There is currently no single therapy that appropriately treats all patients with ED. Thus there is a need for additional noninvasive agents with differing mechanisms of action to offer couples and clinicians more choices for the treatment of erectile dysfunction.

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2.0 Background and History: Uprima

Uprima™ (apomorphine HCl tablets) sublingual will be indicated for the treatment of erectile dysfunction (ED). Apomorphine, the active ingredient of Uprima, has been evaluated for use as a pharmacologic agent since 1869. Apomorphine is synthesized via acid-catalyzed skeletal rearrangement of morphine, with the levo-rotating product, (-) apomorphine, retaining little structural similarity to the narcotic analgesic. Throughout the latter 19th century, apomorphine was used for its emetic properties. Concurrent clinical and animal studies led to further use of apomorphine as an emetic, an antispasmodic, and for the treatment of specific movement disorders and epilepsy.

In the first half of the 20th century, apomorphine was used as a sedative for psychiatric disturbances and as a behavior-altering agent for alcoholics and addicts. By 1967, the dopaminergic effects of apomorphine were recognized and the compound was extensively evaluated for use as an anti-Parkinsonian agent.

Apomorphine is a dopaminergic agonist with affinity for both D_1 and D_2 receptors in sites within the brain known to be involved in the mediation of erection. Studies *in vivo* have shown the erectile function effects of apomorphine are mediated at dopamine receptors in various nuclei in the hypothalamus and midbrain. In particular, the paraventricular nucleus of the hypothalamus has been identified as the site of action. This site may mediate genital and nongenital autonomic aspects of sexual arousal. Oxytocinergic, serotonergic, and possibly nitric oxide signaling may be involved in the cascade of neural events that result from the central action of apomorphine.

Apomorphine acts centrally, and enhances pro-erectile stimuli. In men with stimulation (arousal), the erectogenic effects of apomorphine arise from improved central neural signaling specific to penile vascular response. Mechanistically it is an initiator of erection in rats. However, in men the set point for erectile status is strongly influenced by inhibition and inhibitory pathways. Normal sexual erections are therefore masked by their dependence on pro-sexual stimulation and conditioning appropriate for erection.

Apomorphine has now been specifically formulated in a tablet for sublingual (SL) administration [Uprima™ (apomorphine HCl tablets) sublingual] that has been demonstrated to maintain its erectogenic effects while minimizing the side effects associated with other routes of administration.[1] This new sublingual formulation, Uprima, has been studied in over three thousand (3000) men and shows promise as an option for a wide range of patients with erectile dysfunction.

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3.0 Pharmacology of Uprima

3.1 Physiology and Pharmacology of Erection

Penile erection is a complex neurovascular event which involves coordination of increased arterial flow, sinusoidal smooth muscle relaxation, and decreased venous drainage through the interaction of the brain, nerves, neurotransmitters, smooth and striated muscle and the tunica albuginea.[1] An alteration in any of these components may decrease the response of the erectile tissue, resulting in dysfunction. Other causes of erectile dysfunction include hormonal and psychological disturbances.[2]

Penile erection requires input from autonomic [sacral parasympathetic (pelvic) and thoracolumbar sympathetic (hypogastric and lumbar sympathetic)] and somatic (pudendal) nerves.[3] The parasympathetic nervous system is responsible for vasodilation of the penile vasculature and erection;[4] the response requires proper integration of sensory input from visceral and somatic structures as well as descending input from supraspinal centers which coordinate the autonomic networks responsible for sexual responses.[5] The sympathetic nervous system is responsible for detumescence; this response requires integration of input from pelvic viscera and supraspinal centers.[3] Sympathetic pathways may also be responsible for maintaining erections after injury to parasympathetic pathways. In addition to autonomic innervation, the penis also receives somatic innervation which regulates ejaculatory events[3].

Initiation of penile erection is mediated by two main mechanisms; direct stimulation of the genitalia (reflex erection) or *via* stimuli emanating from the brain (psychogenic erection). Reflex erections are mediated at the spinal level (parasympathetic centers)[6]; the control of psychogenic erections is not well understood and involves higher supraspinal centers.[3] Under normal circumstances, the reflexogenic and psychogenic pathways act in concert to determine the erectile response; this coordination involves a sacral parasympathetic route.

The rate-limiting step in the development of an erection is the ability to achieve corporal smooth muscle relaxation.[6] Immunohistochemical and *in vitro* studies suggest peripheral neurotransmitters are released by nerve fiber endings and are responsible for smooth muscle contraction and relaxation. Antierectile neurotransmitters include noradrenaline[6]; serotonin can be pro- or antierectogenic, depending on the receptor subtype involved.[7,8] Peripheral neurotransmitters that are classified as proerectogenic include acetylcholine and nitric oxide (NO).[6] NO, which is derived from both the vascular endothelium and nerve endings, is believed to be the primary peripheral erectogenic neurotransmitter.[9] Central neurotransmitters which facilitate erection include dopamine and oxytocin.

At the cellular level, smooth muscle relaxation is mediated through the interaction of two distinct pathways involving the second messengers cyclic adenosine or cyclic guanosine monophosphate (cAMP or cGMP). Elevated levels of either cyclic nucleotide ultimately results in an efflux of calcium (Ca^{++}) that leads to smooth muscle relaxation[10].

3.2 Historical Overview

Apomorphine retains little structural similarity to morphine and has none of the addictive or narcotic analgesic properties. It has been used as an emetic, an antispasmodic, a sedative and in the management of Parkinson's disease.[11,12]

It is structurally similar to dopamine[13,14] and has activity at the D1 and D2 dopamine receptor sites[15] which may allow for a more versatile response profile than seen with agents that are specific for a single receptor subtype. It produces a spectrum of behavioral effects that are dependent on dose and route of administration.[16] In the rat, low subcutaneous (s.c.) doses (25-200 μg/kg) induce yawning and penile erection; these responses are often attributed to the activation of dopamine autoreceptors.[17] However, it has also been demonstrated that apomorphine can act *via* postsynaptic dopamine receptors located in the paraventricular nucleus (PVN) of the hypothalamus.[18] High

doses of apomorphine (>200 μg/kg s.c.) elicit stereotyped behaviors which are species-specific and thought to be mediated by the activation of postsynaptic dopaminergic receptors.[19]

3.3 Mechanism of Action

As previously mentioned, apomorphine has been shown to be a nonselective (D1/D2) dopamine receptor agonist with more potent D2-like effects. Central, but not peripheral dopamine receptor antagonists inhibit apomorphine–induced penile erections in rats, suggesting that the erectogenic response is due to a central rather than a peripheral mechanism.[15,20] Both D1 and D2 receptors seem to be involved in this behavior as antagonists specific for each receptor subtype can inhibit the response.

The specific site of action in the brain is believed to be in or providing input to the PVN of the hypothalamus as lesions in this area prevent the apomorphine-induced erectogenic response.[21] It has been postulated that apomorphine activates oxytocinergic neurons in the PVN. The ensuing release of oxytocin causes an increase in intracellular Ca^{++} in these neurons, which in turn leads to an increase in nitric oxide synthase (NOS) activity.[22]

Apomorphine and oxytocin produce comparable effects regarding yawning and erectile response in rats. There is neither additivity nor synergy with co-administration. Central administration of specific oxytocin antagonists had different effects on induced penile erections; that is, with some antagonists, both oxytocin- and apomorphine-induced responses were blocked; other agents were only effective against the effects of oxytocin.[23] This suggests that oxytocin may be involved at different levels of the central nervous system (CNS) for the regulation of these responses.

It has been shown that s.c. administration of apomorphine (80-480 μg/kg) differentially affects plasma and brain levels of oxytocin. Both plasma and hippocampal levels increased, septal levels remained unchanged and hypothalmic levels decreased. These changes were monophasic across the dose range examined and occurred concomitantly

with dose-appropriate, biphasic behavioral responses. Pretreatment with D1/D2 or D2 specific antagonists prevented all of the changes observed in oxytocin concentrations. D1 specific antagonists were only partially able to block the observed increase in plasma levels.[24] These data suggest that the effect of apomorphine on brain levels of oxytocin is mediated by D2 receptors.

Involvement of NOS is supported by the fact that specific inhibitors of this enzyme are able to antagonize both apomorphine- and oxytocin-induced yawning and penile erection. The relative potencies of these compounds in inhibiting apomorphine-induced behavior parallels their ability to inhibit NOS in the brain, suggesting that central NOS is involved in apomorphine-induced erections.[25]

Apomorphine (80 μg/kg s.c.) leads to increases in NO_2^- and NO_3^- concentrations in PVN dialysate; these increases were accompanied by episodes of yawning and penile erection. D1/D2 and D2 antagonists inhibit the apomorphine-induced behavioral response as well as the observed increases in NO_2^- and NO_3^- concentrations, while D1 specific antagonists blocked only the behavioral responses.[26] These data suggest that an increase in NOS activity is involved in the apomorphine-induced behaviors, but that the mechanisms regulating erection and NOS activity are complex and can be independently regulated.

The involvement of Ca^{++} was suggested by the fact that central administration of ω-conotoxin, a selective inhibitor of brain-specific N-type Ca^{++} channels prevented the apomorphine- and oxytocin-induced increase in NO_2^- and NO_3^- concentration in the PVN dialysate as well as penile erection and yawning[22]. Several other Ca^{++} channel blockers were also able to inhibit both apomorphine- and oxytocin-induced episodes of yawning and penile erection.[27] However, the interpretation of the results of these experiments is complicated by the fact that these blockers also affect blood pressure and as such, it may be a hemodynamic effect and not Ca^{++} channel blocking that is responsible for the observed antagonism.

Other areas of the brain which may have a role in apomorphine-mediated responses include the red nucleus (RN) of the ventral midbrain tegmentum (stereotypy and hyperthermy)[28], the nucleus accumbens (yawning and stereotypy)[29] and the pituitary (penile erection).[30]

Involvement of the serontonergic[31] and cholinergic systems has also been implicated as specific inhibitors of both of these pathways and specific neurological lesions can block apomorphine-induced penile erections.

Most adverse effects (stereotypy in animals, nausea, vomiting and syncope in humans) are apparent only at suprapharmacological doses.

The comparison of the results of different experiments is not straightforward given that the outcomes were affected by species, strain, dose, route of administration, relative doses of agonist and antagonist and timing of behavioral observations.

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4.0 Rationale for Recommended Clinical Dosing

The suggested dosing frequency for Uprima is one dose with at least 8 hours between doses. Uprima will be available as a sublingual tablet in three dosage strengths (2, 3, and 4 mg) to be taken on a prn basis.

All doses of Uprima (2, 4, 5 and 6 mg) have been proven to be efficacious for treating erectile dysfunction based on patient and partner assessments in multiple controlled clinical trials. However, little therapeutic gain is noted at doses above 4 mg. Higher doses (5 and 6 mg) are associated with an increased frequency of adverse events. Despite the lack of overwhelming safety issues, the 5 and 6 mg doses will not be recommended for dosing, thus providing a greater safety margin for the use of Uprima.

Apomorphine is rapidly absorbed from Uprima tablets. Measurable concentrations of apomorphine are usually found in plasma within 10 minutes after placing the tablet under the tongue. Apomorphine is also rapidly cleared from the plasma, with the mean concentration usually decreasing to about 10-20% of the maximal values by 4 hours. The harmonic mean for the apparent terminal elimination half-life of apomorphine following the administration of Uprima is approximately 2-3 hours. Hence, only minimal amounts of active drug should remain after 8 hours, thereby justifying safe dosing with Uprima once every 8 hours.

Data from all doses studied in clinical trials will be summarized in this document for both efficacy and safety.

5.0 Clinical Studies Overview

Twenty-seven (27) Phase I-III studies were included in the NDA submitted in June, 1999 and the NDA 4-month safety update submitted in October, 1999. This included 16 Phase I/II studies: a pilot efficacy study, six drug interaction studies (Zofran/Compazine, Antihypertensives/Nitrates, and four alcohol interaction studies), five special population studies (spinal cord injury, post-radical prostatectomy, hepatic-impaired, elderly, and renal-impaired), a radiolabeled metabolism study, a formulation comparison study, and two relative bioavailability/pharmacokinetic studies.

Eleven Phase III studies have been analyzed and are listed in Tables 1 and 2.

Table 1. Phase III Double-Blind Studies

Study Number	N	Treatment Duration	Doses (mg)
Crossover Studies			
M96-470	457	4 weeks	2, 4, 6
M97-658	520	4 weeks	2, 4, 5, 6
M98-941	495	4 weeks	2, 4, 5
M97-804 (Diabetes)	218	4 weeks	4, 5
Parallel Study			
M97-763	569	8 weeks	5, 6 (fixed dose) 2, 4, 5, 6 (dose-optimized)

Table 2. Supportive Phase III Open-Label Dose-Optimization Studies

Study Number	N	Treatment Duration	Doses (mg)
1st Dose Administered at Home Study			
M98-876	151	7 weeks	2, 4, 5
Long-Term Studies			
M96-471	316	6 months	2, 4, 6
M97-659	335	6 months	2, 4, 5, 6
M97-682	489	Up to 3 years	2, 4, 5, 6
M97-793	115	Up to 3 years	2, 4, 5, 6
M98-936	50	Up to 2 years	2, 4, 5, 6

All the studies, with the exception of the three ongoing long-term, open-label studies (M97-682, M97-793, M98-936) are completed and have been fully analyzed. An interim analysis was performed for the three ongoing, long-term, open-label studies so that they could be included in the NDA and the 4-Month Safety Update.

In addition, one open-label first dose at home study with 863 patients was recently conducted to evaluate the effectiveness of written patient instructions in improving the safety profile of Uprima with the recommended optimized dosing regimen (2, 3, and 4 mg). This study has been completed and the study report will be submitted to the FDA in the near future.

6.0 Clinical Pharmacokinetics and Biopharmaceutics Summary

Uprima Formulations. Two Uprima formulations were used in the clinical studies performed by Pentech Pharmaceuticals and TAP Holdings. The first formulation (F1) was developed by Pentech in 2, 4, 6 and 8 mg tablet strengths. Due to issues with the F1 formulation tablets (*e.g.*, physical stability, taste and mouth discoloration), slight changes were made to optimize the Uprima tablet formulation. The second formulation (F2) was manufactured in 2, 3, 4, 5 and 6 mg tablet strengths. Although most of the Phase I pharmacokinetic studies were conducted with the 5 and 6 mg F2 formulation Uprima tablets, 2, 3 and 4 mg tablets are proposed for marketing.

***In Vivo* Uprima Tablet Disintegration/Dissolution.** Significant problems with *in vivo* Uprima tablet disintegration/dissolution occurred in some of the early Phase I studies (M96-599, M97-794, M97-745), but minimal problems were encountered in five later Phase I studies (M98-844, M98-843, M98-815, M98-838, M98-891). In the latter studies, all of which used the F2 formulation tablets, 97% of the tablets, on average, disintegrated or dissolved completely during the 20 minute period when the tablet remained in the subject's mouth. Although the reasons for the improvement in *in vivo* tablet disintegration/dissolution may never be known, the change was temporally correlated with greater emphasis on proper sublingual dosing technique at the Phase I study sites. The percentage of the tablet dissolved was found to be linearly related to the apomorphine concentrations in plasma, with higher AUC values occurring when the tablets dissolved completely (M97-794). The observed correlation was consistent with the presence of substantial amounts of apomorphine remaining in the undissolved portion of the tablets.[1]

Apomorphine Bioavailability from Uprima. The bioavailability of apomorphine from the F2 formulation tablets (2, 4, 5, and 6 mg), relative to a subcutaneous dose (1 mg), was estimated to be 16-18% in a five period crossover study (M98-844). Although the 3 mg tablet was not included in this study, it is within the dose range (2-6 mg) for which dose-

proportionality was established. The estimated 16-18% bioavailability of apomorphine from the F2 formulation tablets is consistent with literature reports of the bioavailability of apomorphine from higher sublingual doses of apomorphine in patients with Parkinson's disease.[2,3,4]

The F1 and F2 formulation tablets have not been shown to be bioequivalent in a pilot comparison study. The bioavailability of apomorphine from the F1 formulation tablets (2, 4 and 6 mg), relative to a subcutaneous dose of apomorphine (1 mg), was estimated to be 6-10% in a four period crossover study (M96-599). However, the mean plasma concentration-time profiles from the F1 tablets were reasonably similar to those found with the F2 formulation tablets in a similarly designed study (M98-844). In contrast, the mean plasma concentrations from the subcutaneous dose of apomorphine in the study with the F1 formulation (M96-599) were considerably higher than those found after subcutaneous administration of apomorphine in the study with the F2 formulation (M98-844). This difference in the apomorphine concentrations after subcutaneous dosing could have contributed to the 2- and 3- fold difference in bioavailability with the two sublingual formulations (*i.e.,* 6-10% vs 16-18%). Another three-period crossover study (M97-794) directly comparing the 6 mg F1 and F2 formulation tablets was also performed and indicated that estimates of apomorphine bioavailability from the F2 formulation tablets were approximately 3-times those from the F2 formulation tablets. However, the failure of most of the F1 formulation tablets to dissolve completely in that study was probably a major factor contributing to the lower bioavailability of apomorphine from the F1 than the F2 formulation.

The effect of food on the bioavailability of apomorphine was not investigated since food intake would not be expected to affect absorption from a sublingual tablet.

Apomorphine Pharmacokinetics. Apomorphine was rapidly absorbed from Uprima tablets. Measurable concentrations of apomorphine were usually found in plasma within 10 minutes and peak concentrations were generally attained within 40-60 minutes after placing the tablet under the tongue. In a five-period crossover study (M98-844) which

compared the 2, 4, 5 and 6 mg F2 tablets to a subcutaneous dose of apomorphine hydrochloride (1 mg), the mean apomorphine C_{max} (0.70-1.9 ng/mL) and AUC_{∞} (1.2-3.6 ng·h/mL) from the sublingual tablets (2-6 mg) were shown to increase in a dose-proportional manner. Subcutaneous administration of apomorphine resulted in a shorter t_{max} (approximately 20 minutes) and higher dose-normalized C_{max} and AUC_{∞} values than sublingual administration.

Most Phase I studies were conducted with the 5 or 6 mg Uprima tablets in order to obtain safety information at the higher doses. In five studies involving 246 subjects who received a 6 mg dose, the mean C_{max} values ranged from 1.4 to 1.9 ng/mL, with an overall mean of 1.6 ng/mL. C_{max} was <1 ng/mL in 59 subjects, between 1 and 2 ng/mL in 139 subjects, between 2 and 4 ng/mL in 43 subjects and >4 ng/mL in 5 subjects. The mean AUC_{∞} values from these five studies were also relatively consistent, ranging from 3.0 to 3.9 ng·h/mL and having an overall mean of 3.4 ng·h/mL. Coefficients of variation for the mean C_{max} and AUC_{∞} values in these five studies were approximately 45-70% and 35-70%, respectively.

Following sublingual administration, apomorphine is rapidly cleared from plasma, with the mean concentrations usually decreasing to about 10-20% of the maximal values by 4 hours. Estimates of the half-life for apomorphine have varied between studies. In early studies where the lower limit of quantitation for apomorphine in plasma was 0.050 ng/mL (M96-599, M97-745) or blood samples were only collected through 6 hours post-dosing (M97-794), the plasma concentrations appeared to decline monoexponentially, with a half-life of about 1 hour. In studies where the lower limit of quantitation for the plasma assay was decreased to 0.0050 ng/mL and the blood collection interval was at least 12 hours (M98-844, M98-843, M98-815, M98-838, M98-891), the apomorphine plasma concentrations in some subjects appeared to decline in a biphasic manner. The terminal phase was not always well-characterized, with the apomorphine concentrations at the later time points tending to fluctuate or even show a secondary increase in a few subjects. In those studies, the harmonic mean for the

apparent terminal elimination half-life of apomorphine following administration of apomorphine SL was approximately 2-3 hours, but the half-life appeared to be substantially longer in a few subjects.

Estimates of the apparent clearance (CL/F) for subcutaneously administered apomorphine were in the range of 3-4 L/h/kg (APO-94-05-01, M96-599, M98-844). Estimates of the apparent volume of distribution (V_z/F) were large and variable, 2-19 L/kg, indicating extensive distribution into tissues (APO-94-05-01, M96-599, M98-844).

***In Vitro* Protein Binding and Distribution into Blood Cells.** At concentrations of 1, 10, 100 and 1000 ng/mL, the *in vitro* human plasma protein binding of radiolabeled apomorphine averaged approximately 88-89%, corresponding to a free fraction of 11-12%.[5] Apomorphine binding was independent of the concentration within that range, was similar in the plasma of males and females, and increased slightly between pH 6.0 and pH 8.0.[12] Studies with individual proteins at physiological concentrations demonstrated that apomorphine (10 ng/mL) was more highly bound to human serum albumin (87.7%) than to α_1-acid glycoprotein (32.9%).[5] Binding in phosphate buffer containing both proteins (87.0%) was similar to that with human serum albumin alone.

The *in vitro* plasma protein binding of [^{14}C]apomorphine (10 ng/mL) averaged 88% in both young (19-40 years old) and elderly (64-82 years old) male subjects. The *in vitro* plasma protein binding of [^{14}C]apomorphine was not consistently or markedly affected in subjects with varying degrees of hepatic impairment (81-86%) or renal impairment (82-85%).

At apomorphine concentrations of 1, 10 and 100 ng/mL, the whole blood/plasma ratio and the cell/plasma ratios were close to unity.[5] In human subjects given a 2 mg sublingual dose of [^{14}C]apomorphine (M98-859), the whole blood to plasma ratio based on total radioactivity averaged 0.6, reflecting the lower distribution of the radiolabeled conjugates of apomorphine into the blood cells.

Metabolism and Excretion. Following sublingual administration of [^{14}C]apomorphine (2 mg as an aqueous solution) (M98-859), the dose was almost quantitatively absorbed and apomorphine was extensively metabolized by sulfation, glucuronidation, and *N*-demethylation. Mass spectral results suggested the presence of both *O*- and *N*-glucuronides and sulfates. *O*-Methylation to give isoapocodeine or apocodeine was a very minor metabolic pathway.

A mean of 93.3% (range: 77.8-108%) of the sublingual carbon-14 dose was excreted in the urine and 16.1% (range: 3.2-39.5%) was eliminated in the feces during the seven-day study period. Urinary excretion was relatively rapid, with mean cumulative totals of 34%, 55%, 66%, 80%, and 91% of the administered radioactivity recovered in the urine at 4, 8, 12, 24 and 48 hours, respectively. Approximately 1.6% of the dose was found in the urine (0-72 h or 0-120 h) as unconjugated apomorphine. About 59% of the dose was excreted in urine as apomorphine sulfates, 12% as apomorphine glucuronides, and 18% as free or conjugated norapomorphine. Metabolites identified in neutral and acid extracts of feces included apomorphine, norapomorphine and their sulfates.

The mean plasma C_{max} for apomorphine occurred sooner but was about 50-fold lower than the C_{max} based on carbon-14 activity. Comparison of the $AUC_{24\,h}$ values indicated that apomorphine accounted for <1% of circulating radioactivity. The major metabolite found in plasma was apomorphine-*O*-sulfate, which represented 63% of the $AUC_{6\,h}$ based on the total radioactivity. Apomorphine-*N*-glucuronide, norapomorphine glucuronide, and apomorphine-*O*-glucuronide comprised 8%, 6%, and 1% of the carbon-14 $AUC_{6\,h}$. These conjugates are not expected to be pharmacologically active.

Studies in mice, rats, and dogs have shown that the apomorphine conjugates are extensively secreted in bile and may be hydrolyzed in the intestinal lumen, thus raising the possibility of enterohepatic circulation. Although the bioavailability of orally administered apomorphine is low, it is possible that small amounts of apomorphine could reach the systemic circulation following hydrolysis of apomorphine conjugates in the

intestinal tract. This process could contribute to the low and variable apomorphine concentrations found in the plasma of some subjects several hours after dosing.

***In Vitro* Metabolism Studies.** Apomorphine was shown to inhibit the activities of cytochrome P450 (CYP) 1A2, 2D6, and 3A, with respective K_i values of 7.4, 27, and 18 μM, but it did not significantly inhibit the activities of CYP2C9 or CYP2C19 at concentrations up to 100 μM.[6] However, the peak apomorphine concentrations from a 6 mg apomorphine SL dose (<2 ng/mL or 0.0075 μM) were at least 1000-fold lower than the K_i values. These *in vitro* results, combined with the "as needed" usage pattern of apomorphine SL, make it is unlikely that apomorphine SL would significantly inhibit the *in vivo* CYP-mediated metabolism of other drugs.

Other *in vitro* studies showed that, although several CYP isoforms could catalyze the *N*-demethylation of apomorphine, CYP1A2, CYP3A, and CYP2C19 appeared to be the principal isoforms responsible for norapomorphine formation.[7] The involvement of several CYP isoforms in the *N*-demethylation of apomorphine, combined with the extensive conjugation of apomorphine, make it unlikely that co-administration of a cytochrome P450 inhibitor would significantly affect the pharmacokinetics of apomorphine.

Apomorphine Pharmacokinetics in Special Population. The pharmacokinetic profile of Uprima (5 mg) was compared in healthy elderly (64-82 years) male subjects and healthy young (19-40 years) male subjects (M98-843). Apomorphine was rapidly absorbed from the sublingual tablets in both age groups. However, the elderly subjects had a 36% longer mean t_{max} (0.95 hour), and a 21% lower mean C_{max} (1.35 ng/mL) than the younger subjects (0.70 hours, and 1.69 ng/mL, respectively). There were no statistically significant age group effects for AUC_t, AUC_∞ or the natural logarithm of λ_z. The longer mean t_{max} and lower mean C_{max} in the elderly subjects than in the young

subjects suggested that the rate of apomorphine absorption was slower in the older subjects. However, the extent of apomorphine bioavailability was not different in the young and elderly subjects.

The pharmacokinetics of apomorphine were studied in male subjects with normal hepatic function and male subjects with mild, moderate or severe hepatic impairment (based on the Child-Pugh classification), who were given single 2 mg and 4 mg doses of apomorphine SL on Days 1 and 7, respectively. Mean C_{max} was estimated to be 16-62% higher and mean AUC_{∞} was estimated to be 35-68% higher in subjects with mild, moderate or severe hepatic impairment than in subjects with normal hepatic function. The upper bound of the 95% confidence intervals suggested that a 2- to 4-fold increase in C_{max} and AUC was possible. The elimination half-life for apomorphine after the 4 mg dose appeared to be slightly longer in the subjects with hepatic impairment (2.9-3.7 hours) than in the subjects with normal hepatic function (1.9 hours).

Male subjects with normal renal function, (CL_{cr} >80 mL/min/1.73 m^2) and male subjects with mild (CL_{cr} >40-80 mL/min/1.73 m^2), moderate (CL_{cr} = 10-40 mL/min/1.73 m^2), or severe (CL_{cr} <10 mL/min/1.73 m^2) renal impairment were given a single 5 mg dose of Uprima. Mean C_{max} was affected little by renal impairment. The mean AUC_{∞} values in the subjects with mild, moderate and severe renal impairment were 4%, 52% and 67% higher than the mean AUC_{∞} in the subjects with normal renal function. The apparent terminal elimination half-life was affected slightly, with a 0.24 hour increase predicted for each 10 mL/min/1.73 m^2 drop in creatinine clearance. Urinary excretion of apomorphine accounted for 0.12-0.16% of the dose in the normal subjects and those with mild or moderate renal impairment, but only 0.006% in the subjects with severe renal impairment.

Drug Interaction Studies. The effects of two commonly prescribed anti-emetics, Zofran® and Compazine®, on the pharmacokinetics of Uprima (6 mg) were investigated in a randomized, open-label, three-period crossover study (M98-815). There were no

statistically significant regimen effects on t_{max}, λ_z or the logarithmically transformed C_{max}, AUC_t and AUC_∞ values. Point estimates and 95% confidence intervals for the bioavailability of Uprima with Zofran® or Uprima with Compazine®, relative to that of Uprima alone, indicated that oral administration of Zofran® or Compazine® had little or no effect on the bioavailability of Uprima (6 mg).

Ingestion of an ethanol (0.3 g/kg) beverage had little, if any, effect on the bioavailability of apomorphine from Uprima 6 mg (M98-838). However, ingestion of a larger amount of ethanol (0.6 g/kg) increased the apomorphine C_{max} by approximately 23% and the AUC_∞ by 12% (M98-891). Administration of Uprima (6 mg) resulted in a slight (8-12%) but statistically significant decrease in the bioavailability of ethanol from a 0.3 g/kg or 0.6 g/kg dose of alcohol (M98-838, M98-891).

6.1 References

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7.0 Summary of Demographics, Study Drug Exposure and Duration of Treatment

7.1 Demographic Characteristics

A total of 2515 male patients participated in Phase II/III studies. Of these, a total of 2379 patients received at least one dose of Uprima. An additional 656 subjects received Uprima in Phase I studies.

Demographic characteristics combined across all Phase II/III studies are summarized in Table 3.

Table 3. Demographic Characteristics: Phase II/III Studies-All Patients Who Received at Least One Dose of Uprima

Variable	N	Mean	Range
Age, years	2379	55.1	(21-76)
Height, inches	2372	70.4	(56-82)
Weight, pounds	2376	199.9	(112-355)
Duration of ED, years	1771	4.8	(0.25-47)

Race	N	(%)
Caucasian	2107	(89)
Black	150	(6)
Hispanic	85	(4)
Asian/Pacific Islander	20	(1)
Other	17	(1)
Subgroup	**N**	**(%)**
Hypertension	717	30.9
Diabetic	367	15.8
Coronary Artery Disease (CAD)	368	15.9
Benign Prostatic Hyperplasia (BPH)	361	15.6
Alcohol Use	1473	63.2
Smoking	363	15.5

Among the 2379 patients in Phase II/III studies who took at least one dose of Uprima, 89% were caucasian and the mean age was 55 years (range 21-76 years, with 90% between 40 and 70 years). Sixteen percent (16%) were tobacco users, 63% periodically consumed alcohol, 16% were diabetics (Type I or Type II), 31% were hypertensive

(documented by a diagnosis of hypertension and/or use of anti-hypertensive medications), 16% had a history of coronary artery disease (documented by a history of MI, by-pass surgery, angioplasty or angina), and 16% had benign prostatic hyperplasia (as documented by medical history). The average duration of erectile dysfunction was 4.8 years, with a range of 3 months to 47 years. The Phase II/III study population appears to be reflective of the overall ED population in the United States.

7.2 Treatment Exposure

Overall, 2379 patients have received at least one dose of Uprima in the Phase II/III studies and took a total of 73,736 doses. A total of 35,394 doses of either 2 or 4 mg (the recommended doses) were taken in the Phase II/III studies. The NDA submissions included data from 461 patients who were exposed to Uprima for at least 6 months and 127 patients who were exposed to Uprima for at least one year.

The extent of exposure for each Uprima dosage group is displayed by number of doses and by number of days in Table 4 and Table 5, respectively.

Table 4. Extent of Uprima Exposure by Number of Doses in Phase II/III Studies

Uprima Dose	Number of Patients Exposed to a Given Number of Doses							Total # of Patients	Total # of Doses
	1	2-8	9-19	20-49	50-100	101-200	>200		
2 mg	39	901	512	95	15	13	1	1576	15891
4 mg	105	746	573	166	35	12	0	1637	19503
5 mg	72	414	448	195	38	11	1	1179	17407
6 mg	78	280	284	203	82	25	3	955	20827
8 mg	36	4	5	0	0	0	0	45	108
Overall*	111	363	802	677	295	111	20	2379	73736

* Each column might not add up to the overall since patients can be exposed to more than one dose level in a study.

Table 5. Extent of Uprima Exposure by Number of Days in Phase II/III Studies

Uprima Dose	Number of Patients Exposed For a Given Number of Days									Total # of Patients
	1-30	31-60	61-90	91-120	121-150	151-180	181-270	271-365	>365	
2 mg	1179	304	33	12	6	10	9	15	8	1576
4 mg	1079	338	90	47	17	14	21	21	10	1637
5 mg	661	287	107	29	30	11	34	14	6	1179
6 mg	421	224	74	54	54	27	52	36	13	955
8 mg	42	3	0	0	0	0	0	0	0	45
Overall*	940	395	191	169	134	89	212	122	127	2379

* Each column might not add up to the overall since patients can be exposed to more than one dose level in a study.

8.0 Summary of the Efficacy of Uprima in the Treatment of Erectile Dysfunction

There are eleven different Phase III efficacy studies discussed in the NDA submissions. An overview of the endpoints for each of these studies is provided in Appendices A and B. Detailed study design descriptions (cross-over, parallel, and open-label) for the eleven studies are provided in Appendix C. The Phase III Crossover studies for the Uprima clinical program were designed in close communication with the FDA.

The efficacy of Uprima has been examined in five controlled Phase III studies: M96-470, M97-658, M98-941, M97-763 and M97-804 (diabetes). The patient population for the first four studies consisted of patients with erectile dysfunction with no major organic component (defined to be patients with erectile dysfunction who still retained some intrinsic penile function and, who did not have such severe organic disease that they would have been unsuitable for participation in a clinical trial). Although patients were to have had no major organic component for the first four studies, many patients had contributing organic etiologies; 28.4% of patients had a prior history of hypertension, 6.9% had diabetes, 15.7% had BPH and 14.4% had coronary artery disease. The M97-804 study restricted enrollment to diabetic patients (Type I and Type II) with erectile dysfunction.

In addition, a brief summary of the efficacy results from five open-label, long-term studies which enrolled patients from previous Phase II/III studies will be presented. However, these were primarily safety studies.

Two different Uprima formulations were used in the Uprima clinical studies. The first "developmental" or F1 formulation was used in the first Phase III controlled study,

M96-470, and its follow-up long-term study (M96-471). Slight changes were made to optimize the Uprima tablet formulation, and an "optimized" or F2 formulation for commercial use was employed in all subsequent Phase III studies.

Results of a Phase I pharmacokinetic (PK) study (M97-794) directly comparing 6 mg F1 and F2 formulation tablets indicated that estimates of apomorphine bioavailability from the F2 formulation tablets were approximately three times that of the F1 formulation tablets. However, these results may have been influenced by the higher percentage of undissolved F1 tablets than F2 tablets. Similar problems with incomplete *in vivo* tablet disintegration or dissolution were not apparent in the large Phase III clinical Study M96-470 which utilized the F1 formulation. The dissolution of the F2 tablets was evaluated in a large Phase III study (M98-941) in which a vast majority of the tablets (99%) dissolved completely within 15 minutes. In two separate relative bioavailability studies (M96-599 and M98-844), the PK profiles for the F1 and F2 sublingual formulations were nearly identical. However, the apomorphine concentrations from the subcutaneous reference doses were different in the two studies, and again resulted in higher estimates of apomorphine bioavailability from the F2 formulation tablets. Thus, conclusions on differences/similarities of apomorphine bioavailability from the two formulations were unclear. However, the efficacy and safety results in Study M96-470 and the other Phase III studies of similar design (M97-658 and M98-941) were extremely similar. Thus, Study M96-470 has been included for completeness. However, it is not considered pivotal by the FDA because the bioequivalence of the F1 and F2 formulations was not proven.

8.1 Efficacy Endpoints

In all Phase III Uprima clinical studies, both patient and partner participation were required on many levels, including informed consent, frequency of intercourse attempts,

and completion of Home-Use and validated questionnaires. In addition, patients and partners received detailed instruction on completion of the Home-Use questionnaires, validated questionnaires, and diaries.

In all Uprima protocols, the primary efficacy endpoint was the number of attempts resulting in an erection firm enough for intercourse as reported by the patient. This was obtained by the patient completing a Home-Use questionnaire after every dose administration in which he was asked a few questions, including:

> Did you attain and maintain an erection firm enough for intercourse?
>
> ____ Yes ____ No

This allowed a direct assessment of efficacy at each dosing attempt. The Home-Use questionnaire was to be completed within 12 hours following intercourse to avoid memory problems often associated with questionnaires which ask patients to recall and somehow average events which occurred over extended periods. Patients were instructed to make at least two attempts at intercourse each week in all Phase III clinical trials.

In addition, TAP felt that the partner's interpretation of the efficacy of the study drug was also a key factor in determining overall efficacy of the drug. Thus, the partner was to independently complete a similar Home-Use questionnaire after every attempt at intercourse. Patients and partners completed these questionnaires both during screening (baseline) and during each treatment period.

There were various additional efficacy endpoints utilized in the Uprima clinical program to assess the efficacy of Uprima. Appendices A and B provide an overview of all efficacy endpoints. At the time of the early trials, the International Index of Erectile Function (IIEF) questionnaire was not available nor was it a validated instrument.

Therefore, the validated Brief Sexual Function Inventory (BSFI)[1] for the patient was utilized in the early studies (M96-470 and M96-471). However, it was recognized that this validated instrument (and the IIEF) evaluated the patient at only one timepoint during the study as opposed to after each attempt. This was regarded as a deficiency and led TAP to design a more "objective" type of evaluation, the Home-Use questionnaire (discussed above), to assess the patient's experience with the study drug after every attempt at intercourse during the treatment period as well as during screening (baseline).

In addition, reflecting TAP's concern for partner benefit, modifications were made to the BSFI for the patient to create a partner questionnaire (Partner-BSFI) which has been subsequently validated.[2]

When the IIEF questionnaire became available as a validated efficacy assessment tool,[3] TAP implemented the questionnaire in the remaining clinical studies. However, the primary endpoint was still based on the patient's assessment on a per attempt basis (Home-Use questionnaire).

In summary, the Uprima clinical program efficacy evaluations encompass both patient and partner assessments of efficacy which include the overall type of validated efficacy questionnaires (BSFI, partner-BSFI, and IIEF) which are completed by the patients and/or partners at the end of treatment and the more "objective" type of efficacy assessments (Home-Use questionnaire) which are completed after each dose of study drug. These types of assessments make it possible to evaluate the consistency and reproducibility of the efficacy response in both the patient's and partner's evaluations.

8.2 Statistical Analysis

Four of the Phase III studies used two-period crossover designs, which were developed in conjunction with the FDA (see Appendix C for a more detailed description of study designs). This is a powerful design because it allows each patient to be his own blinded control. The design requires a stable chronic disease and evaluation for carryover effect

(results of one period affecting a subsequent period). No evidence of carryover effect was detected in the Uprima crossover studies. Thus, with each patient as his own control, these studies directly estimate improvement within a patient based on Uprima treatment compared to placebo and provide much greater precision than similar parallel group studies.

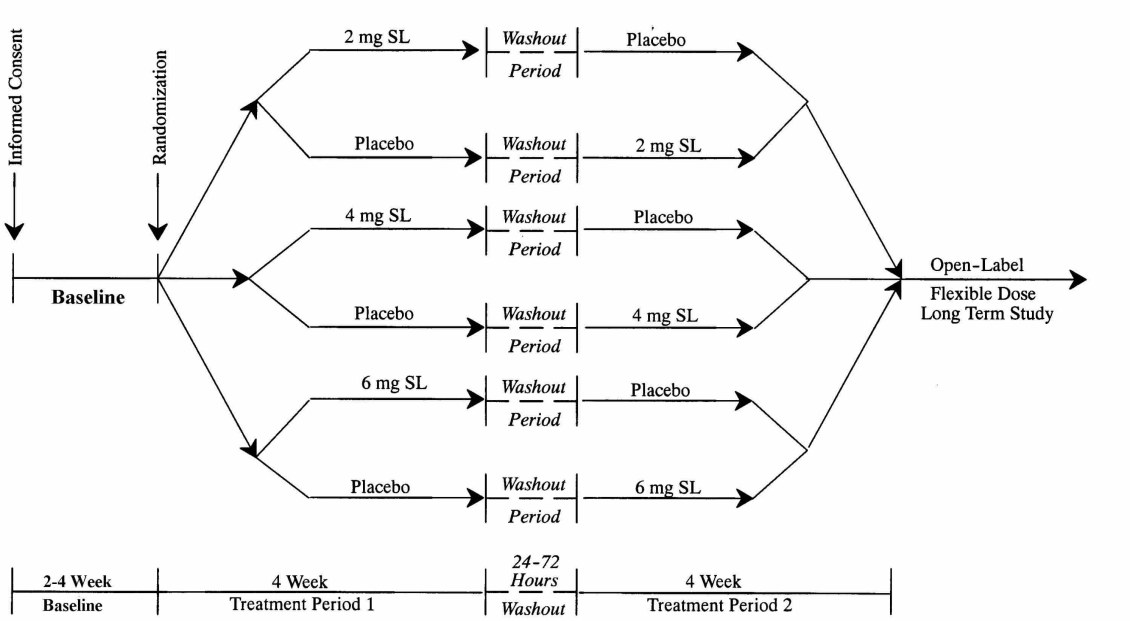
For the crossover studies, the primary analysis of number of attempts resulting in erection firm enough for intercourse (primary endpoint) was a Cochran-Mantel-Haenszel analysis with patients as strata based on all attempts per period (using robust variance estimation suggested by Liang[4]). In the parallel study which involved a dose-optimization period, a one-way analysis of variance with an effect for treatment group based on last eight attempts was the primary analysis of the primary endpoint. Additional analyses done for primary endpoint and statistical methods for other variables are briefly described in Appendix D.

Since one of the strengths of a crossover design is that it allows each patient to serve as his own control, all analyses in the crossover studies are based on patients who have data (at least one attempt) in both crossover periods (i.e., intent-to-treat analyses) unless otherwise specified.

8.3 Phase III Crossover Studies

The efficacy of Uprima has been examined in three double-blind, placebo-controlled Phase III crossover studies which used the same design (M96-470, M97-658 and M98-941). In addition, a fourth crossover study in diabetic patients was conducted and will be discussed in Section 7.4.2. Patients were randomized to receive Uprima for one of the two 4-week treatment periods and placebo in the other treatment period (2, 4 or 6 mg for Study M96-470; 2, 4, 5 or 6 mg for Study M97-658; or 2, 4, or 5 mg for Study M98-941). The entire study duration was 10-12 weeks, including a 2-4 week screening period (baseline). The schematic for a typical study is presented in Figure 1.

Figure 1. Typical Uprima Study Schematic (M96-470)



The target patient population was males, age 18-70 with a diagnosis of erectile dysfunction including patients with contributing organic etiologies. Patients must have had a diagnosis of ED confirmed by the inability to attain and maintain an erection firm enough for intercourse in $\geq$ 50% of attempts for at least 3 months prior to study. Patients were required to be physically able to attain an erection (some intrinsic penile function) as documented by 1) the ability to attain and maintain an erection sufficient for intercourse on some occasion during 3 months prior to the study (i.e., nocturnal/morning erections or masturbation) and 2) nocturnal penile tumescence (NPT) testing with 55% or greater base rigidity for at least 10 minutes on at least one of two nights of NPT testing. The NPT RigiScan testing was reviewed and verified by a central expert RigiScan reader. The study criteria excluded patients with significant organic diseases such as multiple sclerosis, spinal cord injury, radical prostatectomy, past or present penile prosthesis, major penile deformity, hypogonadism, uncontrolled diabetes or uncontrolled hypertension. These inclusion/exclusion criteria resulted in a population that consisted of

a number of patients with organic disease, including patients with diabetes (7.1%), a prior history of hypertension (28.2%), BPH (15.6%), or a history of coronary artery disease (15.2%). In addition, the average duration of ED for those patients was 4.8 years with a range of 3 months to 47 years.

After presenting key efficacy variables (percentage of attempts with erections firm enough for intercourse as evaluated by patient and partner) for each of these studies, a comparison of results across the three studies will be examined for these and other Home-Use questionnaire endpoints. Due to the consistency seen between these studies, additional secondary variables and subgroup analyses will be shown for combined studies only.

8.3.1 Study M96-470: A Phase III Efficacy and Safety Study of Three Fixed Doses of Uprima Tablets Versus Placebo in the Treatment of Male Erectile Dysfunction

The results of the analysis of the proportion of all attempts resulting in an erection firm enough for intercourse showed statistically significantly greater values for all dose levels (2, 4 and 6 mg) of Uprima than for their corresponding placebo doses (based on both patient and partner assessments). These results are shown in Figure 2 and Table 6.

Figure 2. Percentage of All Attempts Resulting in An Erection Firm Enough for Intercourse Based on Patient Responses (Study M96-470)

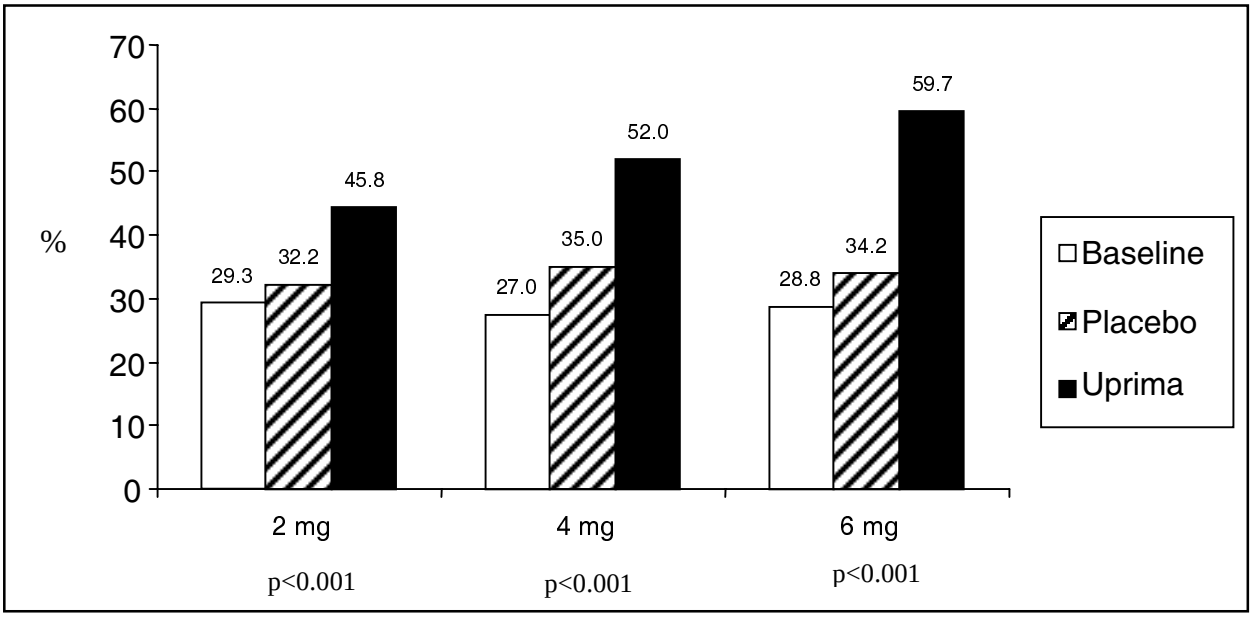


Table 6. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse (Study M96-470)

Rater	Dose (N)	Placebo Success/ Attempts[@]	Placebo Percent	Uprima Success/ Attempts[@]	Uprima Percent	Uprima vs. Placebo p-value
Patient	2 mg (136)	389/1207	32.2	558/1219	45.8	<0.001***
	4 mg (129)	393/1123	35.0	565/1086	52.0	<0.001***
	6 mg (112)	343/1004	34.2	622/1042	59.7	<0.001***
Partner	2 mg (134)	390/1172	33.3	535/1174	45.6	<0.001***
	4 mg (128)	364/1101	33.1	551/1067	51.6	<0.001***
	6 mg (112)	339/1006	33.7	613/1038	59.1	<0.001***

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively

[@] An attempt is defined as the taking of study drug and completion of a home-use questionnaire.

Note: Although percentages of all attempts are shown, p-values come from an analysis adjusting for individual patient. All dose levels were also statistically significant when analyses were done using the first eight attempts of each period instead of all attempts. No suggestion of carryover effect was noted.

8.3.2 Study M97-658: A Phase III Efficacy and Safety Study of Four Fixed Doses of Uprima Tablets Versus Placebo in the Treatment of Male Erectile Dysfunction

This study was identical in design to M96-470 except that it included four dose levels of Uprima (2, 4, 5 and 6 mg). The results of the analysis of the proportion of all attempts resulting in an erection firm enough for intercourse showed statistically significantly greater values for all dose levels (2, 4, 5 and 6 mg) of Uprima than for their corresponding placebo doses (based on both patient and partner assessments). These results are shown in Figure 3 and Table 7.

Figure 3. Percentage of All Attempts Resulting in an Erection Firm Enough for Intercourse Based on Patient Responses (Study M97-658)

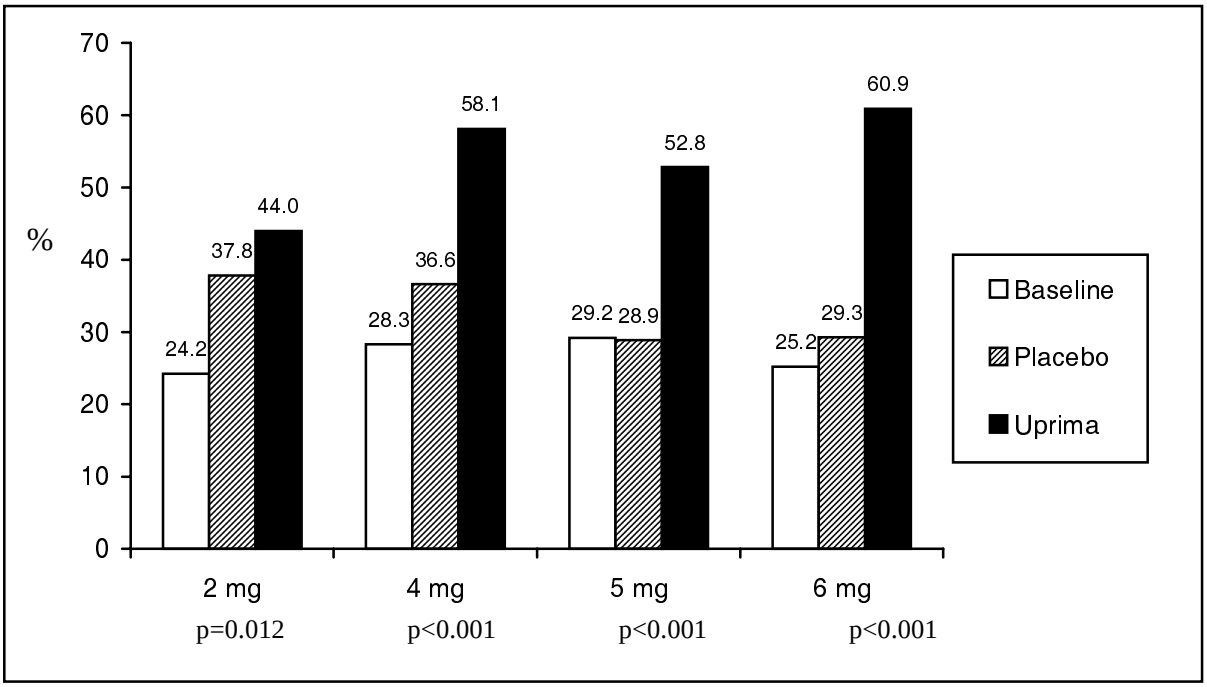


Table 7. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse (Study M97-658)

Rater	Dose (N)	Placebo Success/ Attempts[@]	Placebo Percent	Uprima Success/ Attempts[@]	Uprima Percent	Uprima vs. Placebo p-value
Patient	2 mg (112)	370/980	37.8	432/982	44.0	0.012*
	4 mg (99)	310/848	36.6	519/893	58.1	<0.001***
	5 mg (103)	248/858	28.9	463/877	52.8	<0.001***
	6 mg (87)	211/719	29.3	470/772	60.9	<0.001***
Partner	2 mg (112)	351/966	36.3	427/958	44.6	0.003**
	4 mg (99)	305/843	36.2	519/895	58.0	<0.001***
	5 mg (103)	248/858	28.9	467/877	53.2	<0.001***
	6 mg (87)	211/711	29.7	465/758	61.3	<0.001***

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively

[@] An attempt is defined as the taking of study drug and completion of a home-use questionnaire.

Note: Although percentages of all attempts are shown, p-values come from an analysis adjusting for individual patient. All dose levels were also statistically significant when analyses were done using the first eight attempts of each period instead of all attempts. Across dose groups, no suggestion of carryover effect was noted.

8.3.3 Study M98-941: A Phase III Efficacy and Safety Study of Three Fixed Doses of Uprima Tablets Versus Placebo in the Treatment of Male Erectile Dysfunction

This study was identical in design to the two previous crossover studies, except the doses studied were different. The results of the analysis of the proportion of all attempts resulting in an erection firm enough for intercourse showed statistically significantly greater values for all dose levels (2, 4 and 5 mg) of Uprima than for their corresponding placebo doses (based on both patient and partner assessments). These results are shown in Figure 4 and Table 8.

Figure 4. Percentage of All Attempts Resulting in an Erection Firm Enough for Intercourse Based on Patient Responses (Study M98-941)

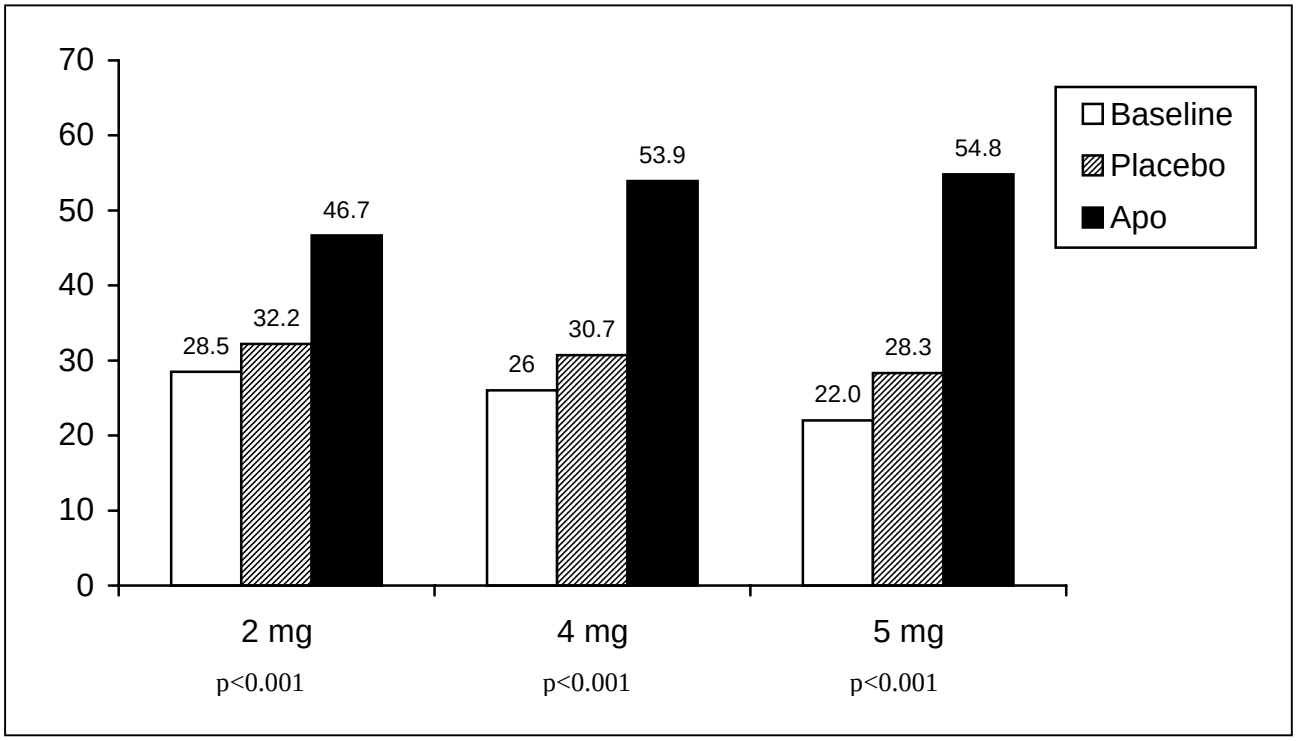


Table 8. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse (Study M98-941)

Rater	Dose (N)	Placebo Success/ Attempts[@]	Placebo Percent	Uprima Success/ Attempts[@]	Uprima Percent	Uprima vs. Placebo p-value
Patient	2 mg (140)	412/1278	32.2	577/1236	46.7	<0.001***
	4 mg (134)	358/1167	30.7	663/1231	53.9	<0.001***
	5 mg (130)	322/1137	28.3	653/1192	54.8	<0.001***
Partner	2 mg (138)	399/1232	32.4	562/1182	47.6	<0.001***
	4 mg (134)	353/1158	30.5	651/1226	53.1	<0.001***
	5 mg (129)	303/1121	27.0	641/1179	54.4	<0.001***

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively

[@] An attempt is defined as the taking of study drug and completion of a home-use questionnaire.

Note: Although percentages of all attempts are shown, p-values come from an analysis adjusting for individual patient. All dose levels were also statistically significant when analyses were done using the first eight attempts of each period instead of all attempts. No suggestion of carryover effect was noted.

8.3.4 Summary of Phase III Crossover Trials

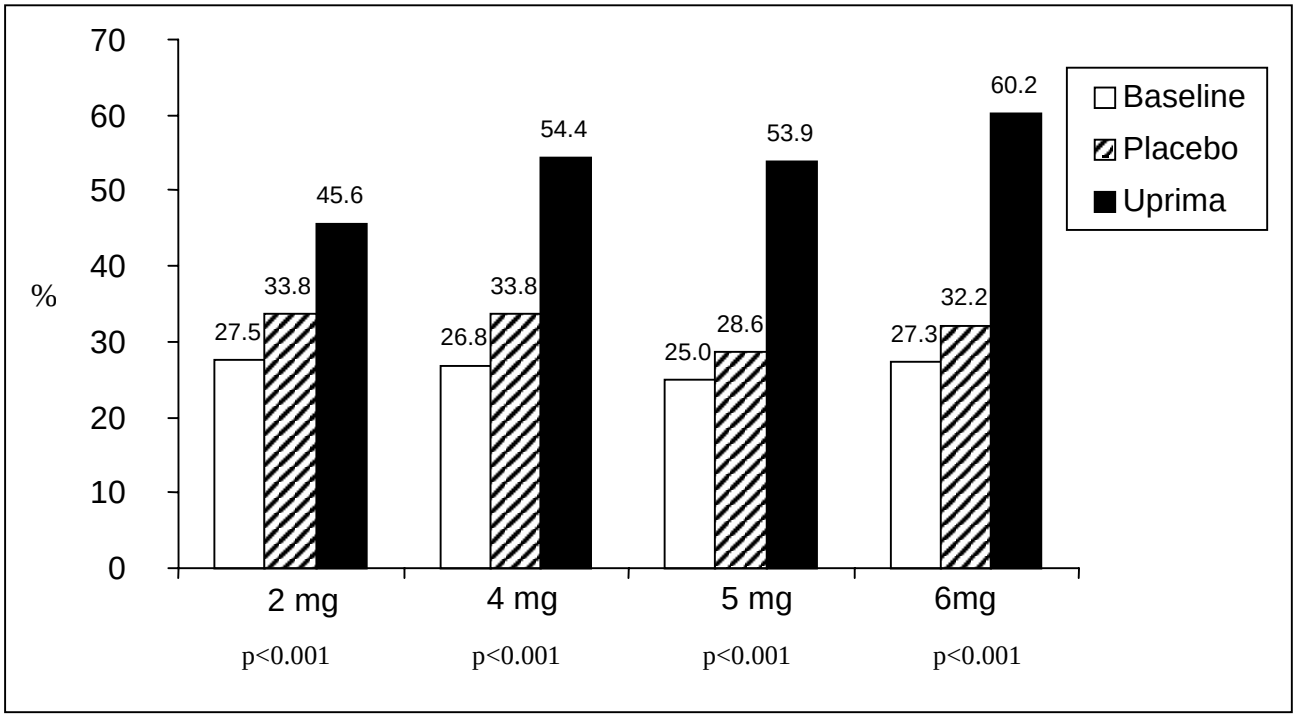
As can be seen from the results of Phase III crossover studies, Uprima at doses of 2, 4, 5 and 6 mg is an efficacious treatment for male erectile dysfunction. The results of the analyses of the key endpoints from the Home-Use questionnaire indicate the consistent superiority of Uprima over placebo.

To illustrate the consistency of these studies, Table 9 shows the percentage of all attempts within each study which resulted in an erection firm enough for intercourse. Overall, the percentages of all attempts resulting in an erection firm enough for intercourse at each dose level were very similar from study to study, ranging from 44.0% to 46.7% for Uprima 2 mg, 52.0% to 58.1% for Uprima 4 mg, 52.8% to 54.8% for Uprima 5 mg and 59.7% to 60.9 for Uprima 6 mg. Figure 5 shows the results using data from all studies combined. The data suggest that there is little therapeutic gain beyond the 4 mg dose.

Table 9. Percent of All Attempts Resulting in an Erection Firm Enough for Intercourse Based on Patient Response (Studies M96-470, M97-658, and M98-941)

	M96-470			M97-658			M98-941			Combined		
Dosage	Baseline	Placebo	Uprima	Baseline	Placebo	Uprima	Baseline	Placebo	Uprima	Baseline	Placebo	Uprima
2 mg	29.3	32.2	45.8	23.9	37.8	44.0	28.5	32.2	46.7	27.5	33.8	45.6
4 mg	27.0	35.0	52.0	28.1	36.6	58.1	26.2	30.7	53.9	26.8	33.8	54.4
5 mg	NA	NA	NA	28.8	28.9	52.8	22.0	28.3	54.8	25.0	28.6	53.9
6 mg	28.8	34.2	59.7	25.3	29.4	60.9	NA	NA	NA	27.3	32.2	60.2

Figure 5. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse Based on Patient Responses (Studies M96-470, M97-658, and M98-941 Combined)



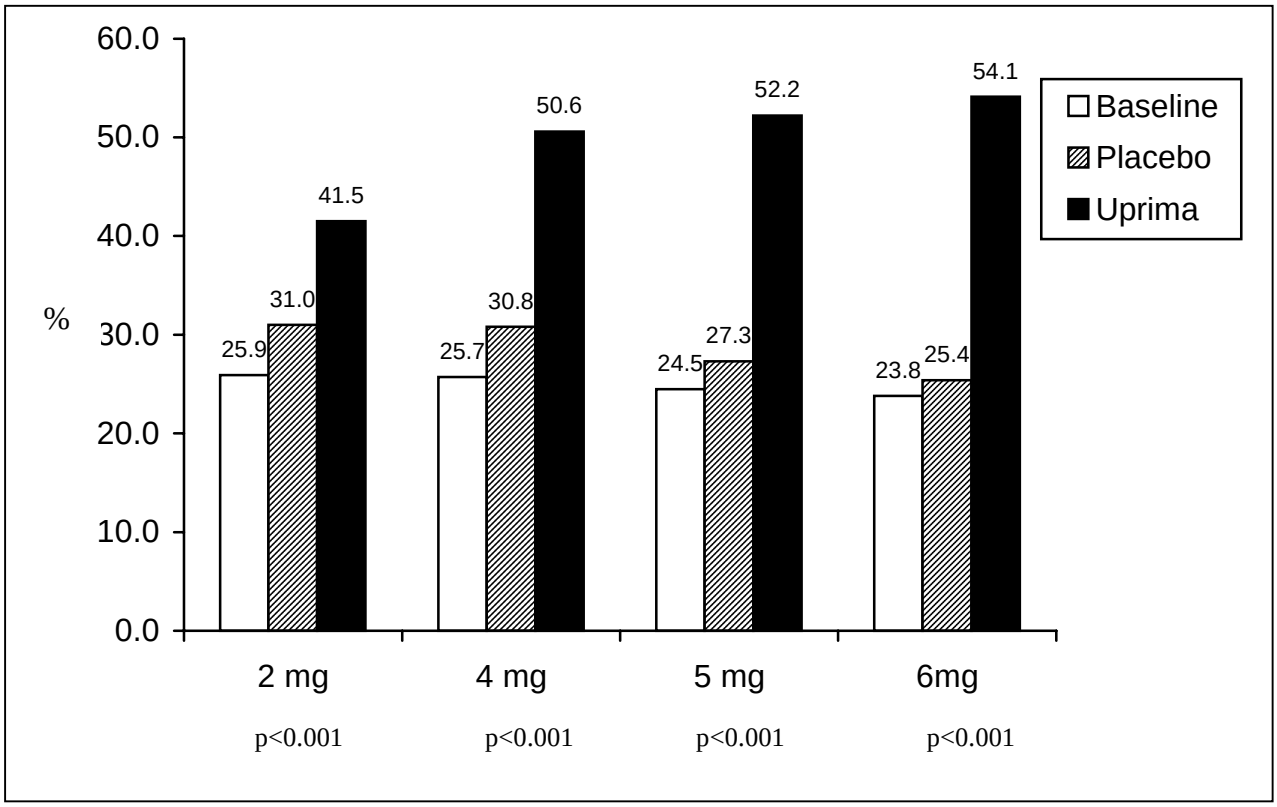
Intercourse Rates

The similarity in study results can also be seen when examining the patient's responses to the question "Did you have intercourse?" Table 10 summarizes these results. As with the primary endpoint, the percentages of all attempts resulting in intercourse at each dose level were very similar from study to study ranging from 38.2% to 44.9% for Uprima 2, 44.0% to 56.0% for Uprima 4 mg, 51.4% to 52.7% for Uprima 5 mg and 51.0% to 58.1% for Uprima 6 mg. Figure 6 shows these values using data from all studies combined. Once again, little therapeutic gain beyond 4 mg is observed.

Table 10. Intercourse Rates Based on Patient Responses (M96-470, M97-658, and M98-941)

Dosage	M96-470			M97-658			M98-941			Combined		
	Baseline	Placebo	Uprima	Baseline	Placebo	Uprima	Baseline	Placebo	Uprima	Baseline	Placebo	Uprima
2 mg	26.2	26.9	38.2	23.8	35.8	41.4	27.5	31.2	44.9	25.9	31.0	41.5
4 mg	23.3	29.0	44.0	26.7	34.4	56.0	26.8	29.9	52.3	25.7	30.8	50.6
5 mg	NA	NA	NA	28.3	27.3	51.4	21.7	27.3	52.7	24.5	27.3	52.2
6 mg	21.9	23.6	51.0	26.0	27.8	58.1	NA	NA	NA	23.6	25.4	54.1

Figure 6. Intercourse Rates Based on Patient Responses (Studies M96-470, M97-658 and M98-941 Combined)



8.3.5 Combined Study Results from Studies M96-470, M97-658 and M98-941

The effectiveness of Uprima in the treatment of erectile dysfunction has been shown to be very consistent across the three independent crossover studies for the key efficacy variables. Additional analyses presented in this section for these and other endpoints use only data from the three crossover studies combined. However, results from the individual studies are consistent with the combined results shown in this section for all efficacy endpoints.

A total of 1182 patients have been evaluated in the three studies combined. A summary of the demographic variables including height, weight, age, and organic contributing factors are provided in Tables 11 and 12 for patients included in the primary efficacy analyses.

Table 11. Demographic Characteristics for Patients Included in the Primary Analysis (Studies M96-470, M97-658 and M98-941 Combined)

Parameter	Uprima 2 mg			Uprima 4 mg			Uprima 5 mg			Uprima 6 mg		
	N	**Mean**	**Range**	**N**	**Mean**	**Range**	**N**	**Mean**	**Range**	**N**	**Mean**	**Range**
Height (Inches)	388	70.3	60-79	362	70.4	59-80	233	70.3	60-79	199	70.6	60-79
Weight (Pounds)	387	198.0	112-307	362	196.6	125-296	233	199.2	119-355	199	199.7	140-286
Age (Years)	388	55.0	26-71	362	54.4	25-74	233	55.3	26-76	199	54.4	25-69
Race	**N**	**(%)**		**N**	**(%)**		**N**	**(%)**		**N**	**(%)**	
Caucasian	345	(88.9%)		320	(88.4%)		203	(87.1%)		177	(88.9%)	
Black	28	(7.2%)		20	(5.5%)		13	(5.6%)		15	(7.5%)	
Hispanic	13	(3.4%)		15	(4.1%)		13	(5.6%)		5	(2.5%)	
Asian/Pacific Islander	0	(0%)		3	(0.8%)		1	(0.4%)		1	(0.5%)	
Other	2	(0.5%)		4	(1.1%)		3	(1.3%)		1	(0.5%)	

Note: Due to rounding, percentages may not add to 100%

Note: Some patients included in the primary analysis were missing baseline values for one or more demographic parameters.

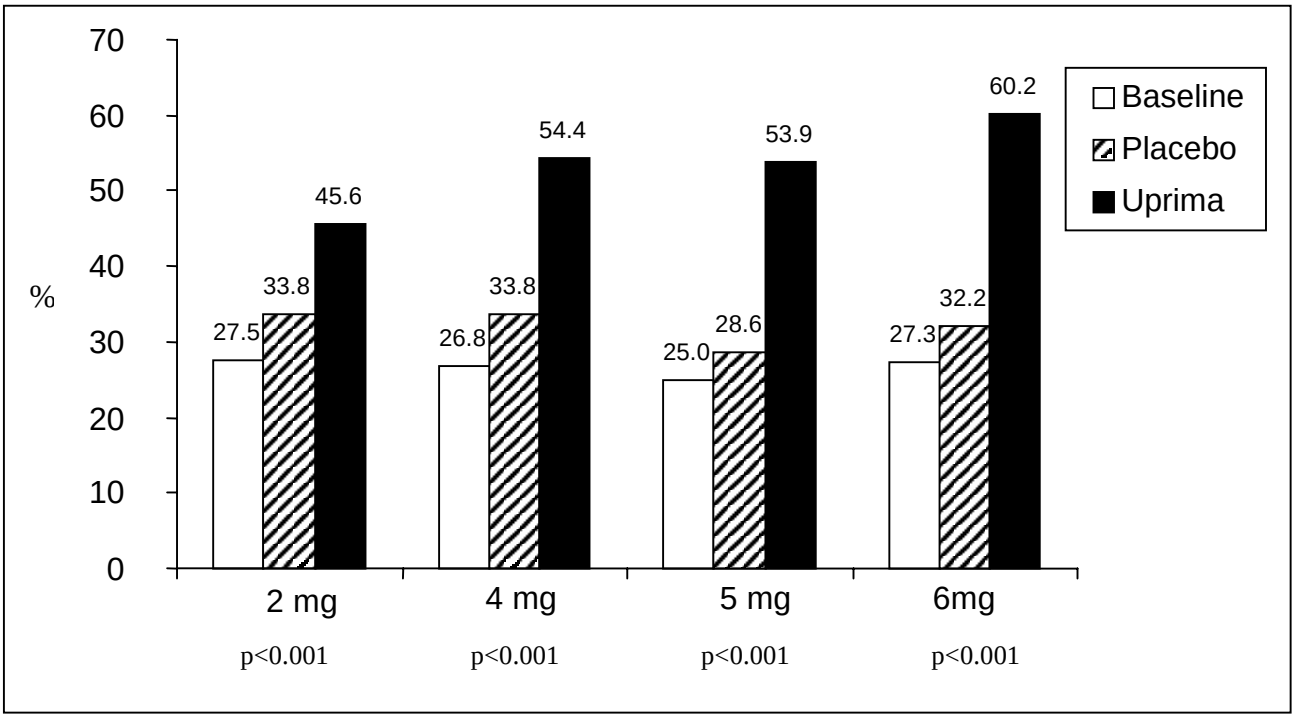
Table 12. Number of Patients with Conditions Associated with ED for Patients Included in Primary Analysis (Studies M97-470, M97-658 and M98-941 Combined)

Condition	Uprima N (%)			
	2 mg	4 mg	5 mg	6 mg
Hypertension	111 (28.6%)	99 (27.4%)	78 (33.4%)	53 (26.6%)
Coronary Artery Disease	60 (15.5%)	50 (13.8%)	32 (13.7%)	31 (15.6%)
Diabetes	30 (7.7%)	23 (6.4%)	25 (10.7%)	8 (4.0%)
BPH	67 (17.3%)	55 (15.2%)	37 (15.9%)	24 (12.1%)

Percentage of Attempts Resulting in Erections Firm Enough for Intercourse (Primary Efficacy)

The results of the analysis of proportion of attempts resulting in an erection firm enough for intercourse showed statistically significantly greater values (all p-values < 0.001) for all four Uprima doses than for their corresponding placebo dosing (based on patient assessments). These results can be seen in Figure 7 below (previously displayed in Figure 5).

Figure 7. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse Based on Patient Responses (Studies M96-470, M97-658, and M98-941 Combined)



Similar results based on partner assessments can be seen in Table 13 which displays the results of both patient and partner analyses. The results of the analyses of percentage of attempts resulting in an erection firm enough for intercourse based on partner assessment yielded statistically significantly greater values (all p-values <0.001) for each of the Uprima dosages than for their corresponding placebo and were virtually identical to those of the patient.

Table 13. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse (Studies M96-470, M97-658 and M98-941 Combined)

		Placebo		Uprima		Uprima vs. Placebo
Rater	Dose (N)	Success/Attempts[@]	%	Success/Attempts[@]	%	p-value
Patient	2 mg (388)	1171/3465	33.8	1567/3437	45.6	<0.001***
	4 mg (362)	1061/3138	33.8	1747/3210	54.4	<0.001***
	5 mg (233)	570/1995	28.6	1116/2069	53.9	<0.001***
	6 mg (199)	554/1723	32.2	1092/1814	60.2	<0.001***
Partner	2 mg (384)	1140/3370	33.8	1524/3314	46.0	<0.001***
	4 mg (361)	1022/3102	32.9	1721/3188	54.0	<0.001***
	5 mg (232)	551/1979	27.8	1108/2056	53.9	<0.001***
	6 mg (199)	550/1717	32.0	1078/1796	60.0	<0.001***

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively.

[@] An attempt is defined as the taking of study drug and completion of a home-use questionnaire.

Note: Although percentages of all attempts are shown, p-values come from an analysis adjusting for individual patient. All dose levels were also statistically significant when analyses were done using the first eight attempts of each period instead of all attempts. No suggestion of carryover effect was noted.

When all the above analyses are performed using only each patient's first eight attempts (instead of all attempts) the results are identical with respect to statistical significance with only minor differences in estimated values noted. Analyses of sequence effects within each dose level were also performed for these data; no statistical significance was noted. Therefore, there is no suggestion of carryover effects that could confound the conclusions from these analyses. Nevertheless, an analysis of first period data was performed and all doses were statistically significant compared to placebo.

Treatment Success

Analyses of the percentages of patients classified as a treatment "success" were performed using both patient and partner assessments. A patient is classified as a "success" for a treatment if at least 50% of all his attempts using that treatment resulted in erections firm enough for intercourse. The results of these analyses yielded a statistically significantly greater (all p-values < 0.001) proportion of successful patients

on each of the four Uprima doses than for placebo no matter which assessments were used (patient and partner data were extremely consistent). These results can be seen in Table 14 below.

Table 14. Percentage of Patients Classified as a Treatment Success (Studies M96-470, M97-658 and M98-941 Combined)

		Placebo		Uprima		
Rater	Dose (N)	Number of Successful Pts.	%	Number of Successful Pts.	%	p-value
Patient	2 mg (388)	140	36.1	185	47.7	<0.001***
	4 mg (362)	126	34.8	215	59.4	<0.001***
	5 mg (233)	72	30.9	135	57.9	<0.001***
	6 mg (199)	64	32.2	128	64.3	<0.001***
Partner	2 mg (384)	136	35.4	184	47.9	<0.001***
	4 mg (361)	124	34.3	209	57.9	<0.001***
	5 mg (232)	69	29.7	137	59.1	<0.001***
	6 mg (199)	65	32.7	130	65.3	<0.001***

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively

The use of 50% of attempts resulting in erections firm enough for intercourse as the definition of treatment "success" was chosen *a priori* (protocol specified) and reflected the inclusion criteria for these studies. It should be noted that no matter what percentage of attempts is used as a "success" cut-off, the estimated percentage of patients classified as a success is larger for each dosage level of Uprima than for placebo. For example, this can be seen for the 2 and 4 mg data in Figures 8 and 9, respectively. Although the plots are not shown for 5 and 6 mg, the results are similar. For any percentage level of attempts used to define "success" (x-axis), the percentage of patients achieving greater than that percentage of success (y-axis) can be determined from the plot.

Figure 8. Erection Firm Enough for Intercourse – Uprima 2 mg (Studies M96-470, M97-658 and M98-941 Combined)

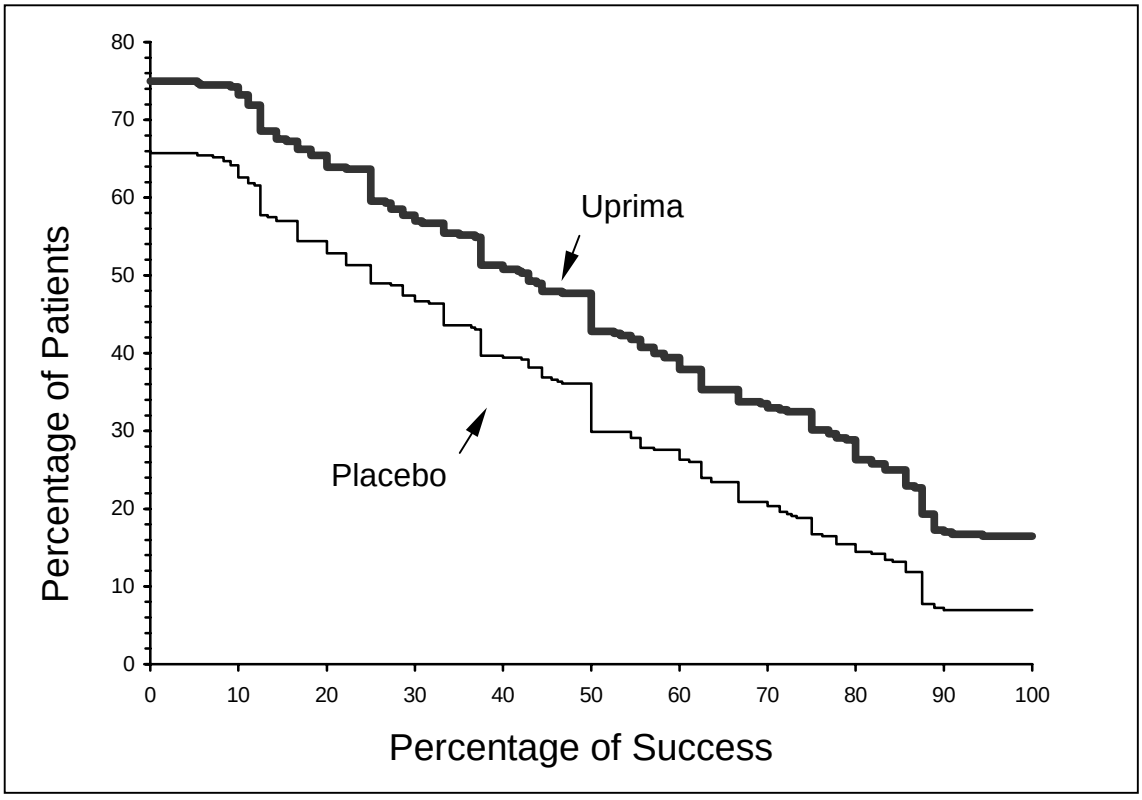
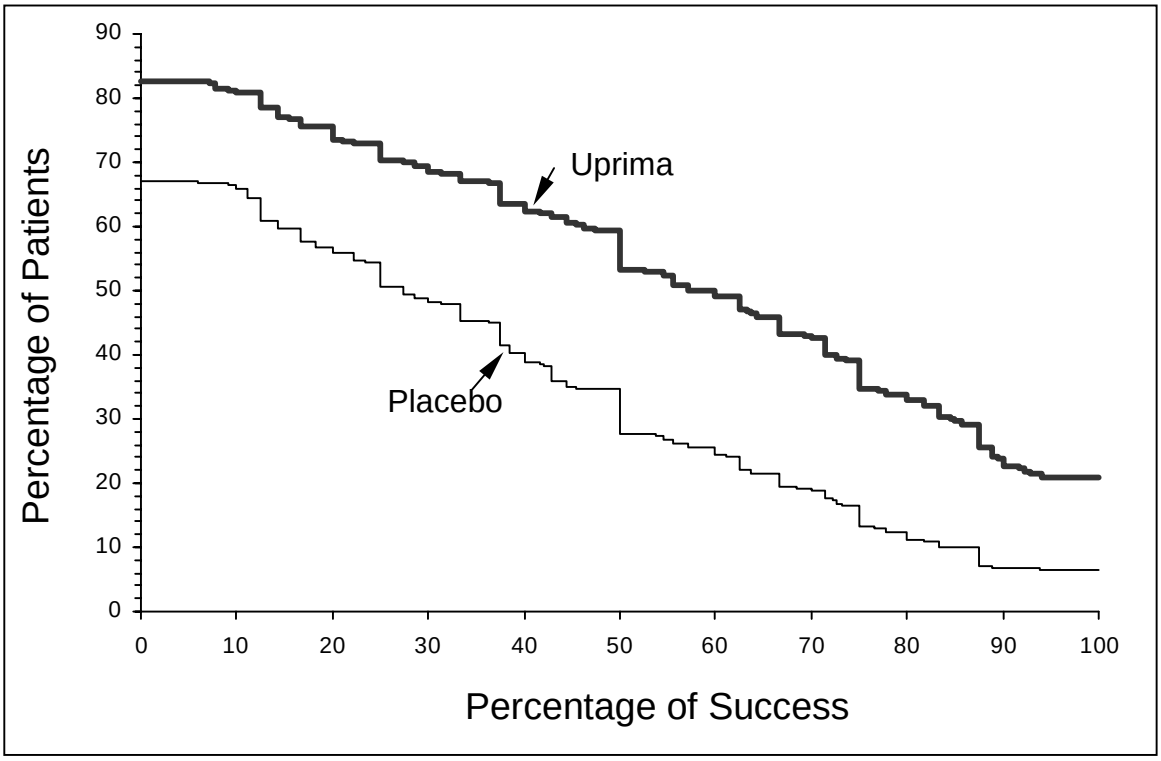


Figure 9. Erection Firm Enough for Intercourse – Uprima 4 mg (Studies M96-470, M97-658 and M98-941 Combined)



Intercourse Rates

The results of the analysis of percentage of attempts resulting in intercourse showed statistically significantly greater values (p-values < 0.001) for all four Uprima doses than for their corresponding placebo dosing based on patient assessments. These results can be seen in Figure 10 (previously shown in Figure 6) as well as in Table 15.

Figure 10. Intercourse Rates Based on Patient Responses (Studies M96-470, M97-658 and M98-941 Combined)

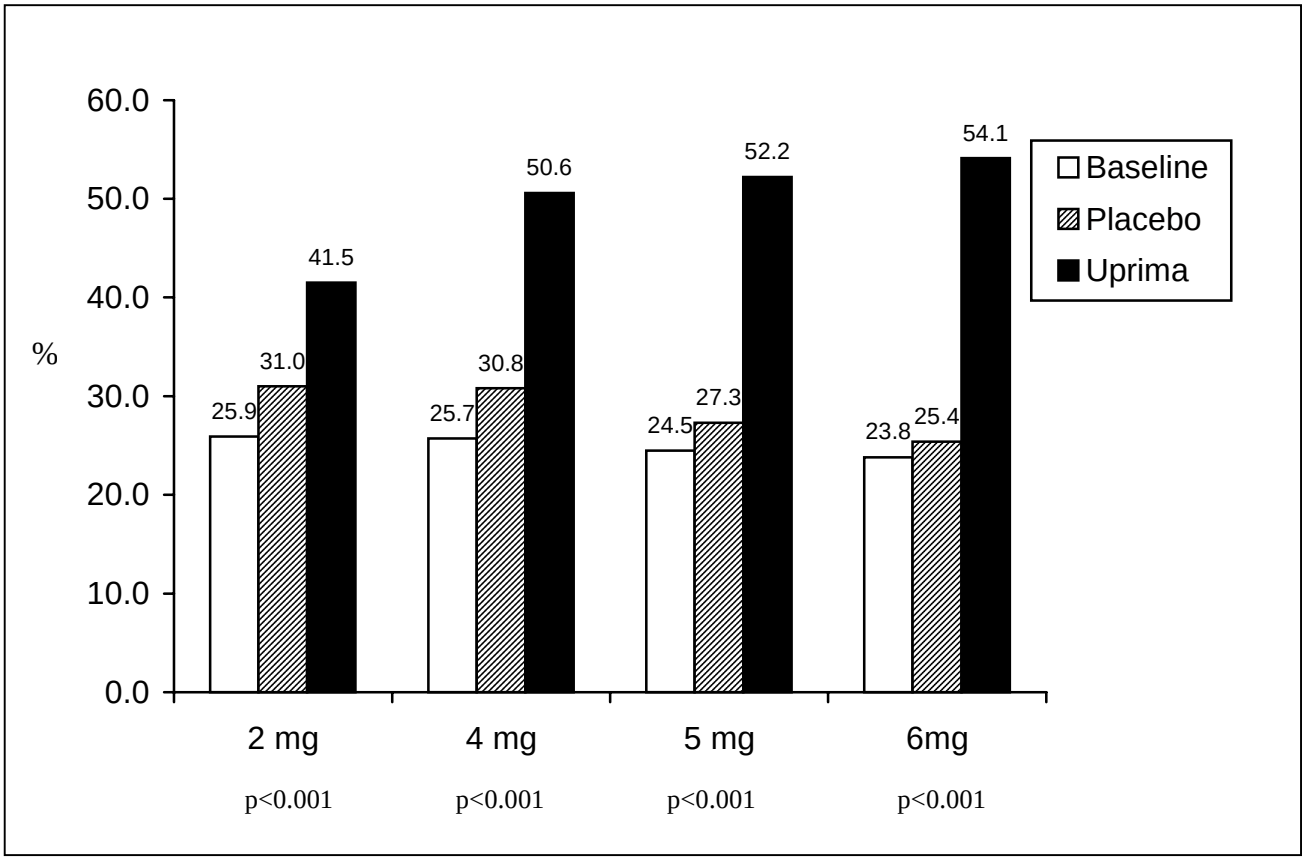


Table 15. Percentage of Attempts Resulting in Intercourse (Studies M96-470, M96-658 and M98-941 Combined)

Rater	Dose (N)	Placebo Success/Attempts[@]	Placebo %	Uprima Success/Attempts[@]	Uprima %	p-value
Patient	2 mg (387)	1061/3420	31.0	1406/3385	41.5	<0.001***
	4 mg (361)	957/3103	30.8	1602/3169	50.6	<0.001***
	5 mg (233)	541/1982	27.3	1068/2047	52.2	<0.001***
	6 mg (199)	425/1676	25.4	949/1754	54.1	<0.001***
Partner	2 mg (383)	1026/3318	30.9	1369/3266	41.9	<0.001***
	4 mg (360)	933/3057	30.5	1565/3119	50.2	<0.001***
	5 mg (232)	543/1965	27.6	1064/2031	52.4	<0.001***
	6 mg (199)	441/1682	26.2	961/1748	55.0	<0.001***

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively

[@] An attempt is defined as the taking of study drug and completion of a home-use questionnaire.

Note: Although percentages of all attempts are shown, p-values come from an analysis adjusting for individual patient. All dose levels were also statistically significant when analyses were done using the first eight attempts of each period instead of all attempts. No suggestion of carryover effect was noted.

Satisfaction with Attempt at Intercourse

After each attempt at intercourse, patients recorded their satisfaction with that attempt on a five point scale ranging from very dissatisfied (0) to very satisfied (4). The results of the analyses of average satisfaction across attempts yielded statistically significantly larger mean average satisfaction values (p-values <0.001) for each of the four Uprima dosages than for their corresponding placebo, based on both patient and partner assessments.

One way to look at this improvement is to consider the number of patients on each treatment who showed an average improvement in average satisfaction of one or more points over their baseline values. The percentage of patients who had at least a one point average improvement over baseline was statistically significantly larger for each Uprima dose than for their corresponding placebo. Figures 11 and 12 show these results.

Figure 11. Percentage of Patients with a 1 Point Improvement in Average Satisfaction Based on Patient Responses (Studies M96-470, M97-658 and M98-941 Combined)

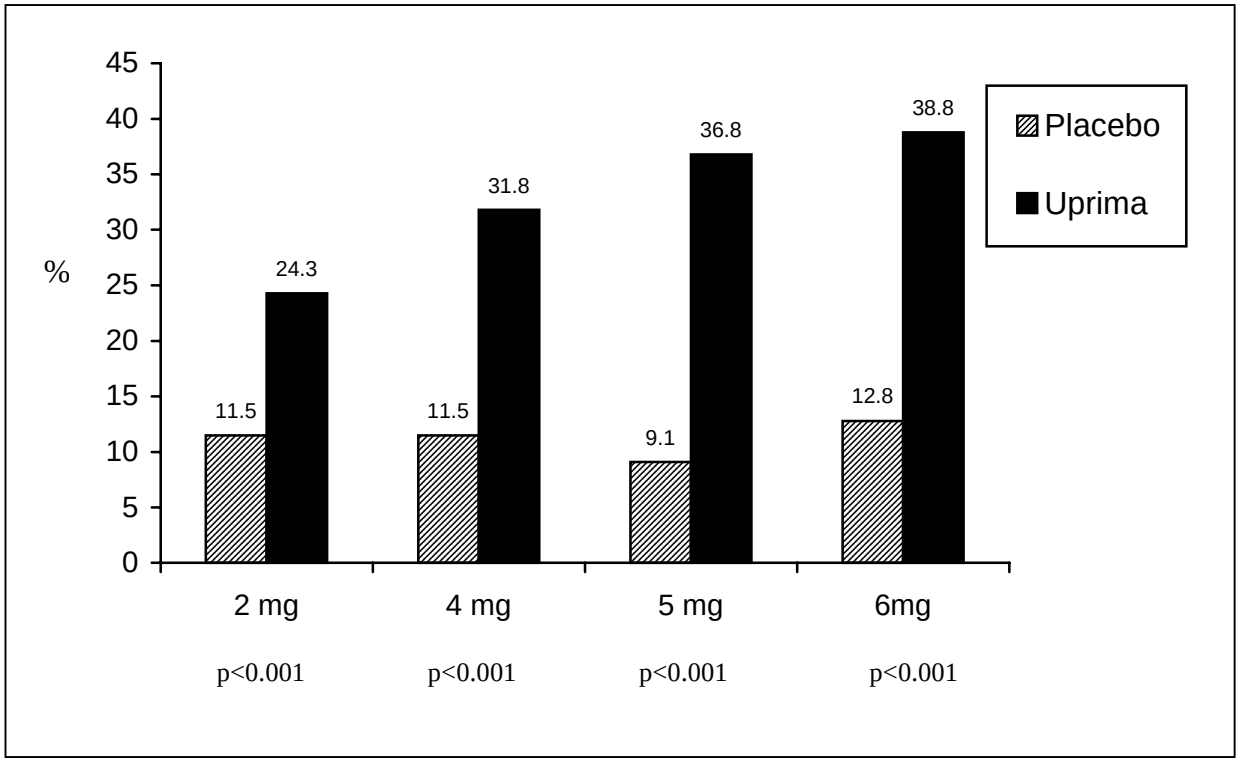
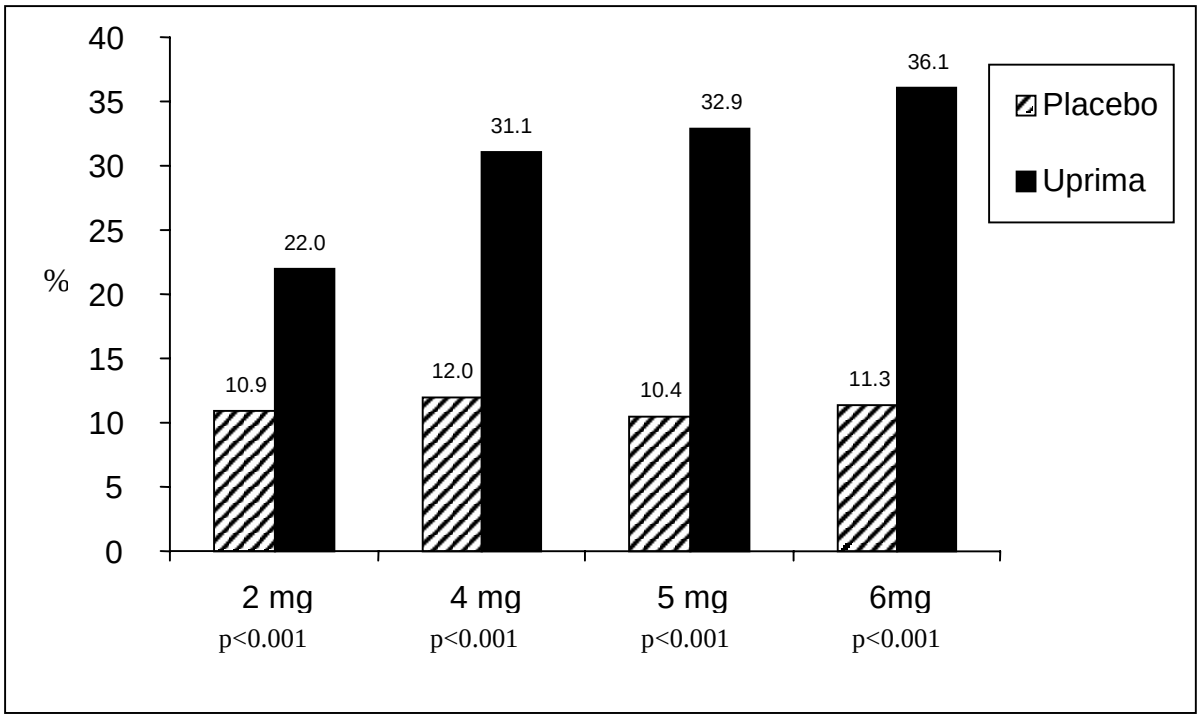


Figure 12. Percentage of Patients with a 1 Point Improvement in Average Satisfaction Based on Partner Responses (Studies M96-470, M97-658 and M98-941 Combined)



Time Until Erection

After each dosing attempt, patients recorded their estimate of the time from the moment they placed the tablet under their tongue until the time an erection was achieved. The results of the analysis of median time to erection, based only on attempts where an erection occurred, can be seen in Table 16. Although many more erections occurred on Uprima, when an erection did occur, the time to erection was quite similar for Uprima and placebo. This suggests that an erection induced by Uprima is similar to a natural erection in time to occurrence.

Table 16. Median Average Time to Erection (Based on the Average of All Attempts Where an Erection Occurred) (Studies M96-470, M97-658 and M98-941 Combined)

	Placebo		Uprima	
Dose (N)	Median (Minutes)	95% Confidence Interval	Median (Minutes)	95% Confidence Interval
2 mg (245)	16.7	15.0 – 18.0	17.5	15.6 – 19.0
4 mg (246)	15.0	13.8 – 17.8	16.0	13.9 – 17.5
5 mg (147)	20.0	17.5 – 24.0	19.0	16.0 – 20.0
6 mg (126)	15.0	11.7 - 18.0	16.0	13.3 - 20.0

Duration of Erection

When using only attempts resulting in an erection, the mean duration of erection was statistically significantly longer for each of the Uprima dosages than for placebo (ranging from 11.0 to 13.9 minutes for Uprima versus 9.1 to 9.9 minutes for placebo). The results can be seen in Table 17. Significant differences were also observed for analyses based on all attempts. This suggests that in addition to more erections occurring with Uprima, as shown in previous analyses, the duration of the erections occurring with Uprima is longer than those with placebo.

Table 17. Mean Average Duration of Erection (Based on the Average of All Attempts Where an Erection Occurred) (Studies M96-470, M97-658 and M98-941 Combined)

Uprima Dose (N)	Placebo Mean	Uprima Mean	p-value
2 mg (308)	9.2	11.0	<0.001***
4 mg (317)	9.9	12.7	<0.001***
5 mg (191)	9.7	13.9	<0.001***
6 mg (176)	9.1	13.1	<0.001***

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively

Brief Sexual Function Inventory (BSFI) for the Patient

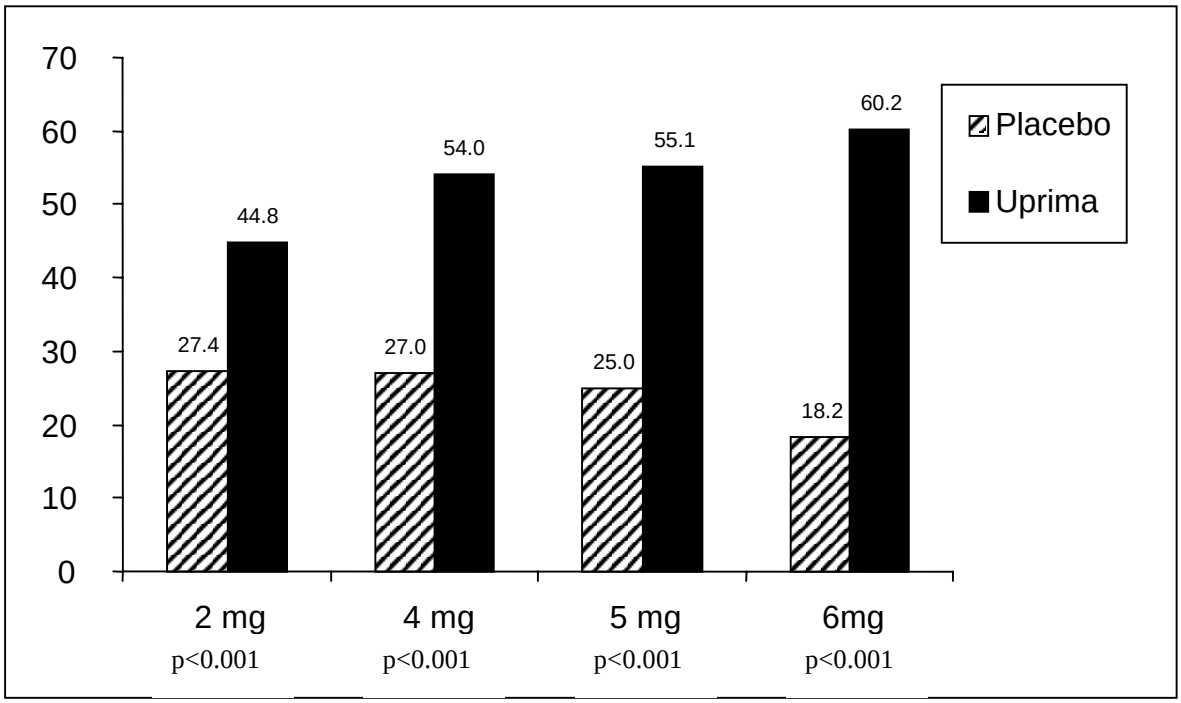
During the M96-470 Study, each patient completed a BSFI. This questionnaire is a validated measure of patient perception of erectile functioning. Individual answers to the BSFI were combined to create two indices – the index of erectile function and the index of satisfaction. In this single study, the results of the analyses of mean BSFI indices yielded statistically significant improvements for all three Uprima doses versus placebo for both the indices ($\leq$ 0.002).

International Index of Erectile Function (IIEF)

In studies M97-658 and M98-941, the IIEF was used; the combined data from these studies are presented below. Statistically significant improvements ($p<0.001$) were shown consistently across all four Uprima dose groups in the following four domains: erectile function, intercourse satisfaction, overall satisfaction and orgasmic function. The fifth domain, sexual desire, was statistically significant for the 5 mg dose group only ($p<0.001$); however, this was not representative of a dose-dependent trend and the magnitude of the effect was quite small (0.3 on a scale of 2-10). Therefore, this result is not considered clinically significant. Some statistical significance was found in the sequence effect analyses within each dose level, but there were no consistent patterns. Therefore, there is no suggestion of carryover effects that might confound the conclusions from these analyses.

Since a four point change in the index of erectile function is considered clinically significant[5], an analysis was done summarizing the percentage of patients in each dose group who had at least a four point improvement from baseline. The percentage of patients with at least a four point improvement in erectile function was statistically significantly larger for each Uprima dose than for the corresponding placebo. These results are shown in Figure 13.

Figure 13. Percentage of Patients with a 4 Point Improvement in Erectile Function (IIEF) (Studies M97-658 and M98-941 Combined)[@]



[@] The IIEF was not utilized in Study M96-470.

Partner Brief Sexual Function Inventory

During the M96-470, M97-658 and M98-941 studies, each patient's partner completed a partner version of the BSFI. This questionnaire was shown in these studies to correspond quite well with the patient BSFI and is considered a validated measure of partner perception of erectile functioning. Individual answers to the partner BSFI were combined to create two indices – the index of erectile function and the index of satisfaction. The results of the analyses of mean partner BSFI indices yielded statistically significant improvements for all four Uprima doses versus placebo for both indices ($p \leq 0.001$).

One way to illustrate these improvements is to consider the number of partners on each treatment who recorded an improvement of one point or greater over baseline for each BSFI index. For both the erectile function and satisfaction indices, the percentage of partners who reported at least a one point improvement over baseline was statistically significantly larger for each Uprima dose than for their corresponding placebo. These results are shown in Figures 14 and 15.

Figure 14. Percentage of Patients with 1 Point Improvement in Erection Rating (Partner BSFI) (Studies M96-470, M97-658 and M98-941 Combined)

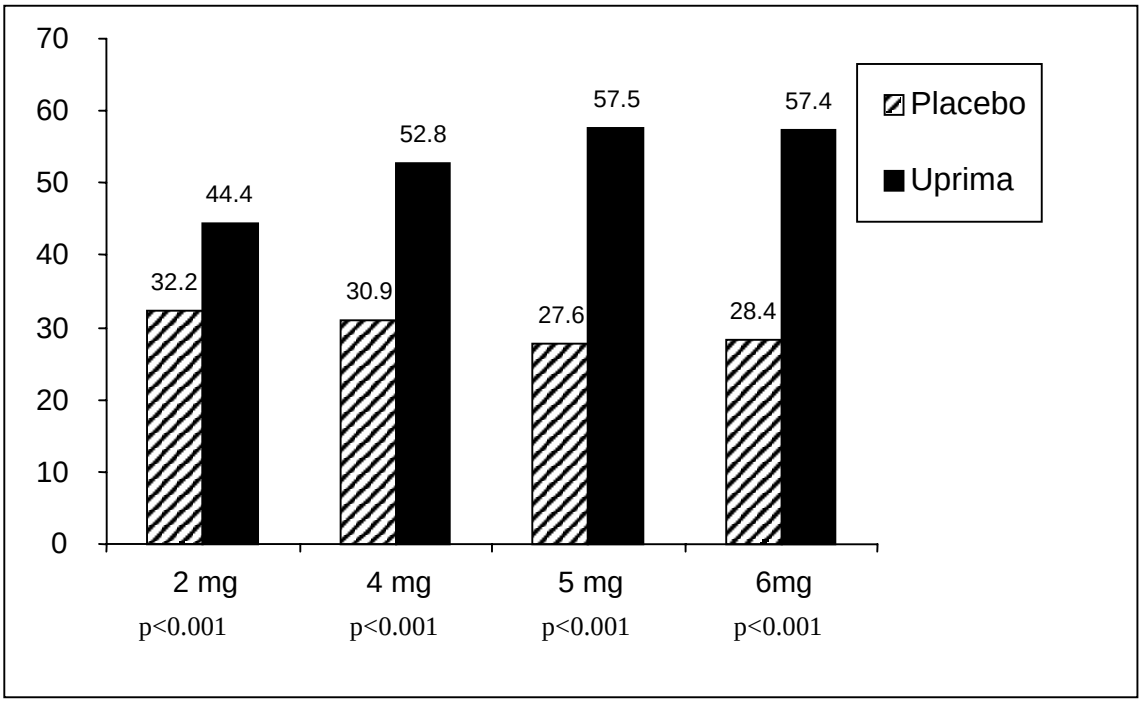
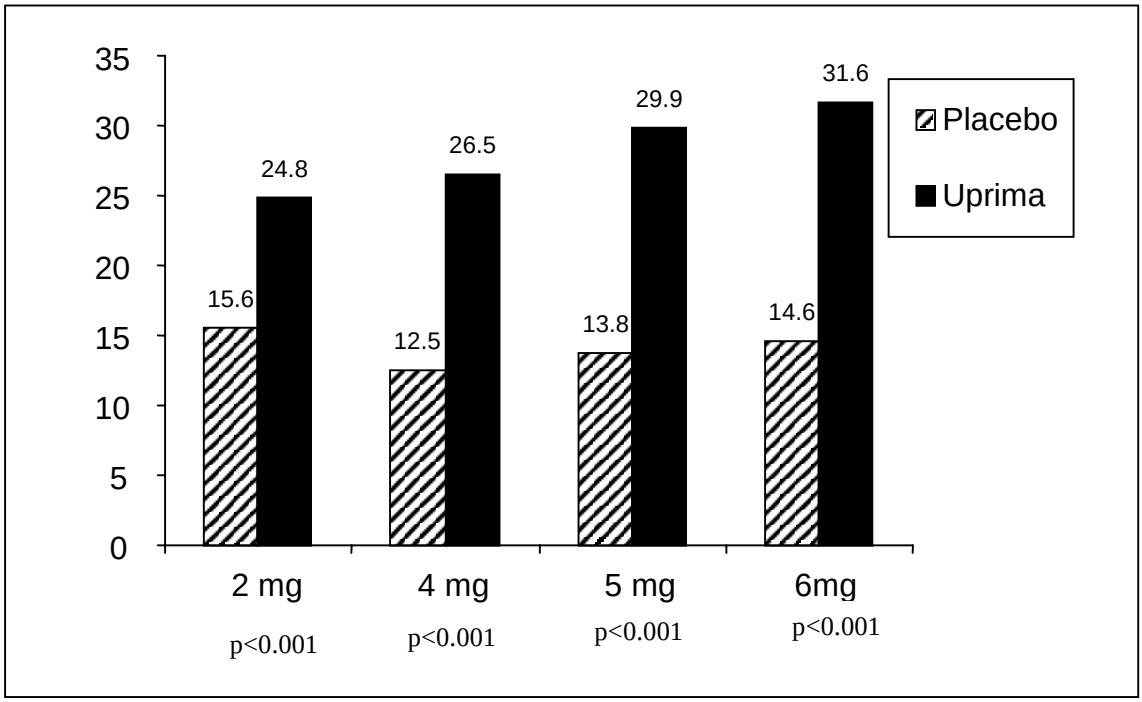


Figure 15. Percentage of Patients with 1 Point Improvement in Satisfaction Rating (Partner BSFI) (Studies M96-470, M97-658 and M98-941 Combined)



RigiScan Assessment

To ensure patients had some intrinsic penile function, all sites in these studies performed nocturnal penile tumescence (NPT) testing at screening. In addition, at 10 sites in Study M96-470, "in-office" RigiScan assessments were performed as an objective evaluation of the effects of Uprima and placebo, although overall this included less than 50 patients per dose group. The procedure was performed in a clinical setting during which each patient viewed a pre-selected erotic video. The results of the analysis of mean RigiScan parameters yielded numerically higher means for the 4 and 6 mg Uprima doses than for placebo for all parameters. These differences were statistically significant for all five parameters for the 6 mg Uprima dose. Two of the differences over placebo (mean maximum base rigidity and mean maximum tip rigidity) for the 4 mg Uprima dose were significant. There were no statistically significant differences from placebo in mean

RigiScan parameters for the 2 mg Uprima dose. Despite the artificial setting, modest sample sizes, and limitations of RigiScan testing, these objective data are supportive of the efficacy of Uprima.

Subgroup Analyses

Subgroup analyses based on the primary endpoint (percent of erections firm enough for intercourse) were performed for patients with different baseline ED severities. In addition, subgroup analyses were performed in patients with hypertension, diabetes, coronary artery disease, and benign prostatic hyperplasia as well as alcohol users, smokers and elderly patients.

Baseline ED Severity (IIEF)

In both M97-658 and M98-941, patients completed the IIEF questionnaire. Using the method suggested by Rosen[6], each patient's current level of erectile function can be classified. Patients can fall into one of five categories based on the sum of their scores from questions 1-5 and 15 of the IIEF: unevaluable, no ED (>25), mild (17-25), moderate (11-16), or severe (<10) erectile dysfunction. The unevaluable category includes patients who either did not answer one of the six questions or answered one of the questions as "did not attempt intercourse." The baseline ED severity for Studies M97-658 and M98-941 combined is shown in Table 18.

Table 18. Baseline IIEF Erectile Dysfunction Severity/All Randomized Patients Included in the Primary Efficacy Analysis (Studies M97-658 and M98-941 Combined*)

Erectile Dysfunction Based on IIEF	Uprima N (%)			
	2 mg	4 mg	5 mg	6 mg
Mild	60 (23.7%)	55 (23.6%)	57 (24.5%)	23 (26.4%)
Moderate	88 (34.8%)	87 (37.3%)	83 (35.6%)	28 (32.2%)
Severe	91 (36.4%)	77 (33.1%)	74 (31.8%)	30 (34.5%)
No Erectile Dysfunction	2 (0.8%)	1 (0.4%)	1 (0.4%)	0
Unevaluable	11 (4.4%)	13 (5.6%)	18 (7.7%)	6 (6.9%)

* IIEF not utilized in M96-470.

Analyses of the primary endpoint were performed for each baseline IIEF severity and are shown in Table 19. The decreasing placebo rates with increasing severity clearly show that the IIEF severity and the percentage of attempts resulting in an erection firm enough for intercourse are strongly related. For patients with moderate and severe erectile dysfunction, statistical significance was achieved for all four Uprima doses compared to placebo. For the mild subgroup, statistical significance was observed for 5 and 6 mg while numerical improvements almost reaching statistical significance were noted for 2 and 4 mg. The relatively small number of patients with mild ED may have precluded significant findings in the 2 and 4 mg doses, even though the therapeutic gains were similar to those seen for the moderate and severe groups. The results of these analyses are shown in Table 19.

Table 19. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse by Baseline IIEF Severity (Studies M97-658 and M98-941 Combined)

	Dose (N)	Placebo	Uprima	p-value
Mild	2 mg (60)	61.1	70.0	0.082
	4 mg (55)	58.1	69.9	0.061
	5 mg (57)	52.1	77.1	<0.001***
	6 mg (23)	62.7	80.8	0.012**
Moderate	2 mg (88)	38.6	52.9	<0.001***
	4 mg (87)	31.4	60.4	<0.001***
	5 mg (83)	30.2	62.3	<0.001***
	6 mg (28)	31.2	64.5	<0.001***
Severe	2 mg (91)	17.5	25.2	0.003**
	4 mg (77)	21.2	42.3	<0.001***
	5 mg (74)	15.1	36.8	<0.001***
	6 mg (30)	10.6	56.8	<0.001***

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively

Additional Subgroup Analyses

Subgroup analyses of the percentage of attempts resulting in an erection firm enough for intercourse based on all attempts were performed for patients reporting hypertension (documented by a diagnosis of hypertension and/or use of hypertensive medications), coronary artery disease (CAD, documented by a history of MI, by-pass surgery, angioplasty, or angina), benign prostatic hyperplasia (BPH, as documented in patient medical history) or diabetes (Type I or II) as well as for alcohol users, smokers and elderly patients (>65 years). Statistical significance was seen for all four dose levels in the hypertension, CAD, BPH, alcohol user and elderly subgroups. Numerical improvements, reaching or nearly reaching statistical significance, favoring Uprima over placebo were also seen for all four dose levels in the diabetes and smoking subgroups. The small sample sizes in the latter two subgroups appear to explain the lack of statistically significant findings at some dose levels. The results of the subgroup analyses are presented for the recommended doses (2 and 4 mg) in the following table.

Table 20. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse – Subgroup Analyses (Studies M96-470, M97-658, and M98-941 Combined)

	2 mg Group				4 mg Group			
Subgroup	**N**	**Placebo**	**Uprima**	**p-value**	**N**	**Placebo**	**Uprima**	**p-value**
Hypertension	111	34.5	44.9	.001***	99	28.7	47.8	<.001***
Diabetes	30	22.4	40.3	.038*	23	31.8	48.2	.074
Coronary Artery Disease	60	25.8	40.7	.003**	50	24.7	54.3	<.001***
Benign Prostatic Hyperplasia	67	37.7	57.7	<.001***	55	28.6	52.0	<.001***
Alcohol Use	267	35.4	44.7	<.001***	243	35.6	54.4	<.001***
Elderly (>65 years)	52	25.1	33.3	.027*	38	32.2	53.6	<.001***
Smoking	53	40.8	48.7	.090	69	41.6	55.9	.007**

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively

8.4 Additional Controlled Studies

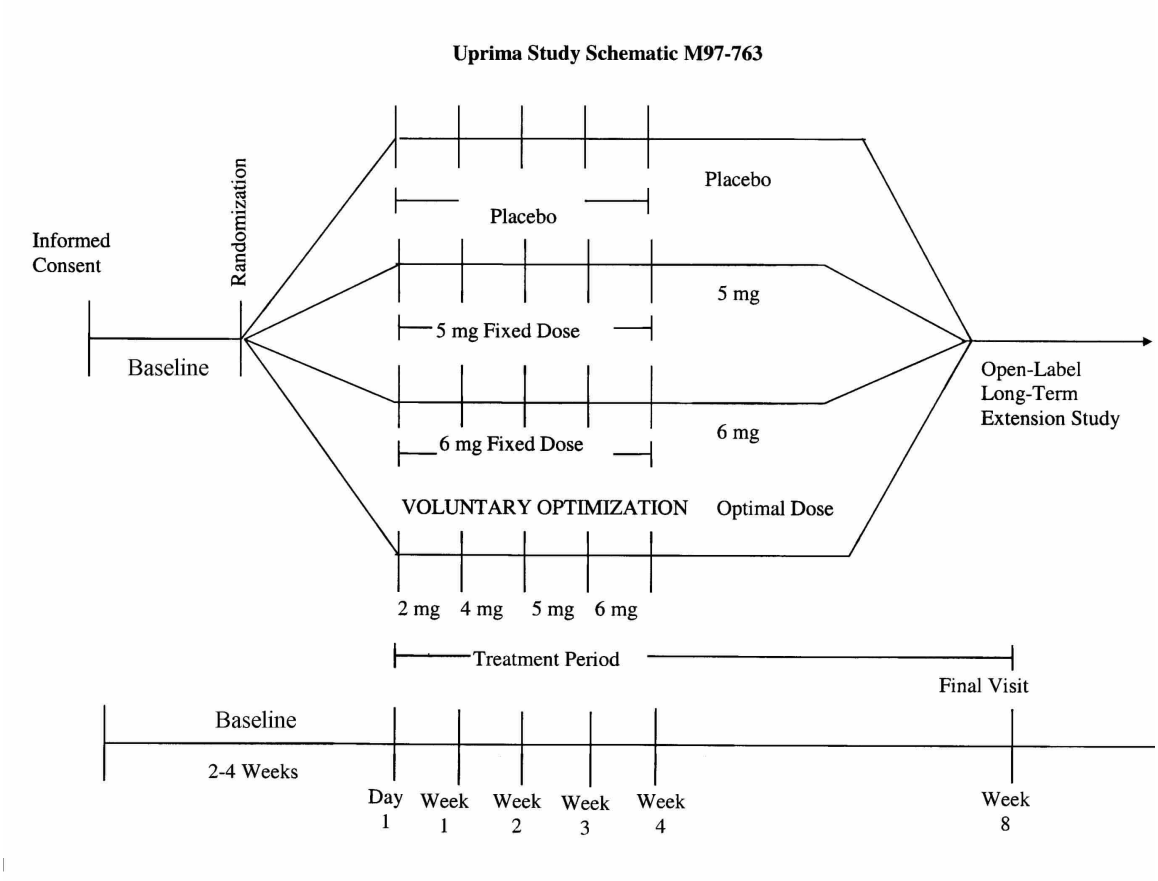
Two other controlled studies were included in the NDA. Study M97-763 evaluated the same population as the Phase III crossover studies, but investigated a dose-optimization (voluntary titration) regimen in a parallel-group study. Study M97-804 was similar in design to the three crossover studies but enrolled only diabetic patients with ED. Results from these studies are described in this section.

8.4.1 Study M97-763: A Phase III Efficacy and Safety Study Comparing Escalating Doses of Uprima or Placebo in the Treatment of Male Erectile Dysfunction

The Phase III parallel study (M97-763) was double-blind and placebo-controlled. Patients were randomized to one of four groups (a voluntary optimization regimen consisting of 2, 4, 5 and 6 mg Uprima, 5 mg fixed dose of Uprima, 6 mg fixed dose of Uprima or placebo). Optimization occurred during the first 4 weeks of treatment. During the last four weeks of the eight-week treatment period, patients continued on their optimal dose determined during the first four weeks of treatment. Since all groups were blinded to their treatment regimen, the investigator could attempt to increase or decrease

the patient's dose in a stepwise manner due to lack of efficacy or unacceptable side effects. The entire study duration was 10-12 weeks, including a 2-4 week screening period. The schematic for this study is presented in Figure 16.

Figure 16. Uprima Study Schematic M97-763



Patients enrolled in the study were asked to make at least 8 attempts during the last 4 weeks (dose maintenance period) which followed the 4-week dose optimization period. The primary efficacy endpoint as well as other home-use efficacy endpoints were analyzed using one-way analysis of variance based on the patient's last 8 attempts. For patients who finish the study and follow the protocol, these last eight attempts should take place after they have increased to their optimal dose.

A total of 569 patients received study drug in this trial (242 in the Uprima dose optimization group, 89 in the 6 mg fixed dose group, 119 in the 5 mg fixed dose group, and 119 in the placebo group). Of the patients in the dose-optimization group, 78% optimized their dose up to 5 or 6 mg. In addition to the analyses comparing each dose group to placebo, analyses of the dose-optimization group were performed using only attempts made while on 2 or 4 mg.

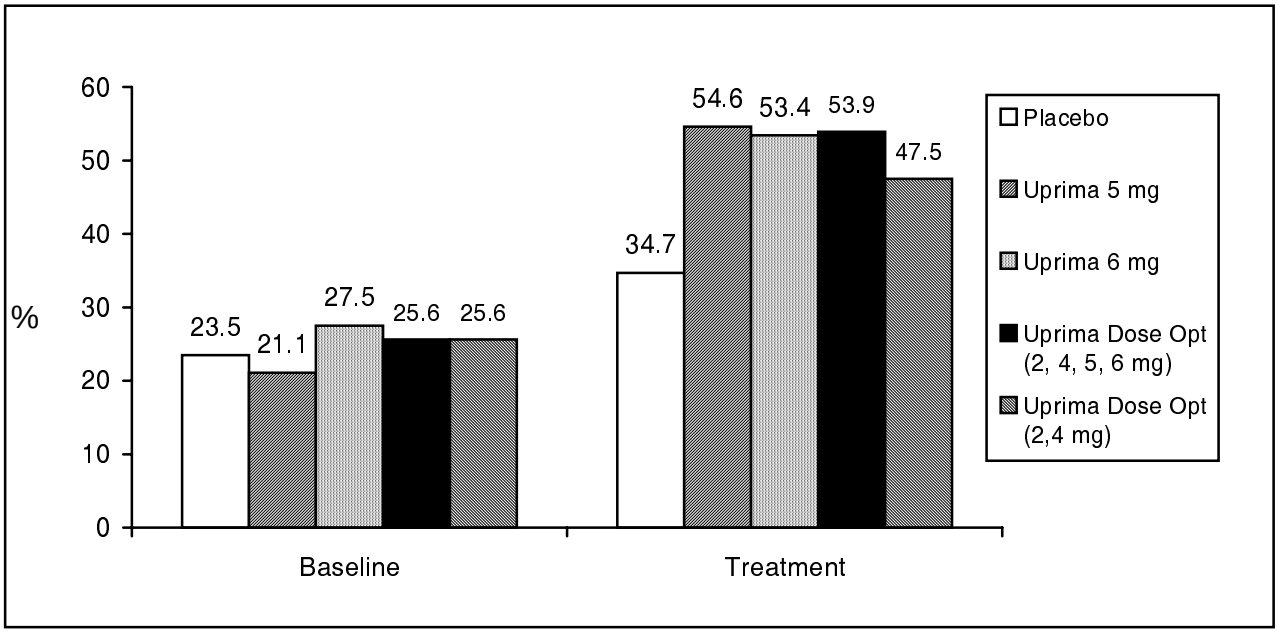
The demographic data for this study were similar to that seen in previous studies already discussed in this report; therefore, it is not presented in detail in this report. The data from the patient home-use questionnaires are presented below.

Percentage of Attempts with Erection Firm Enough for Intercourse (Primary Efficacy)

Analysis of the mean percentages of attempts between each of the Uprima treatment groups versus placebo for the last eight attempts resulting in an erection firm enough for intercourse showed statistically significantly greater mean percentages (p-values $\leq$ 0.002) for all three Uprima treatment groups (53 to 55%) than for placebo (35%) based on both patient and partner assessments. Results from the partner assessment were similar ($p \leq 0.019$). In addition, a similar analysis of the Uprima dose-optimization group versus placebo was performed including only those attempts for patients while they were on 2 or 4 mg. For this analysis, the Uprima group had a statistically significantly higher mean

percentage of erections firm enough for intercourse (48%) as compared to the placebo group (35%) based on both the patient and partner assessments (p-value $\leq$ 0.004). These results are shown in Figure 17.

Figure 17. Average Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse (Based on Last Eight Attempts) – Patient Data (Study M97-763)



An additional analysis was performed at FDA's request using all attempts which occurred during the dose maintenance period (the last four weeks). During this period, patients within the Uprima dose-optimization group should have been on their optimum dose. Furthermore, an analyses using all attempts during the study was performed. As in the analysis based on the last eight attempts, the results of both of these analyses yielded statistically significantly higher mean percentages versus placebo for all apomorphine groups.

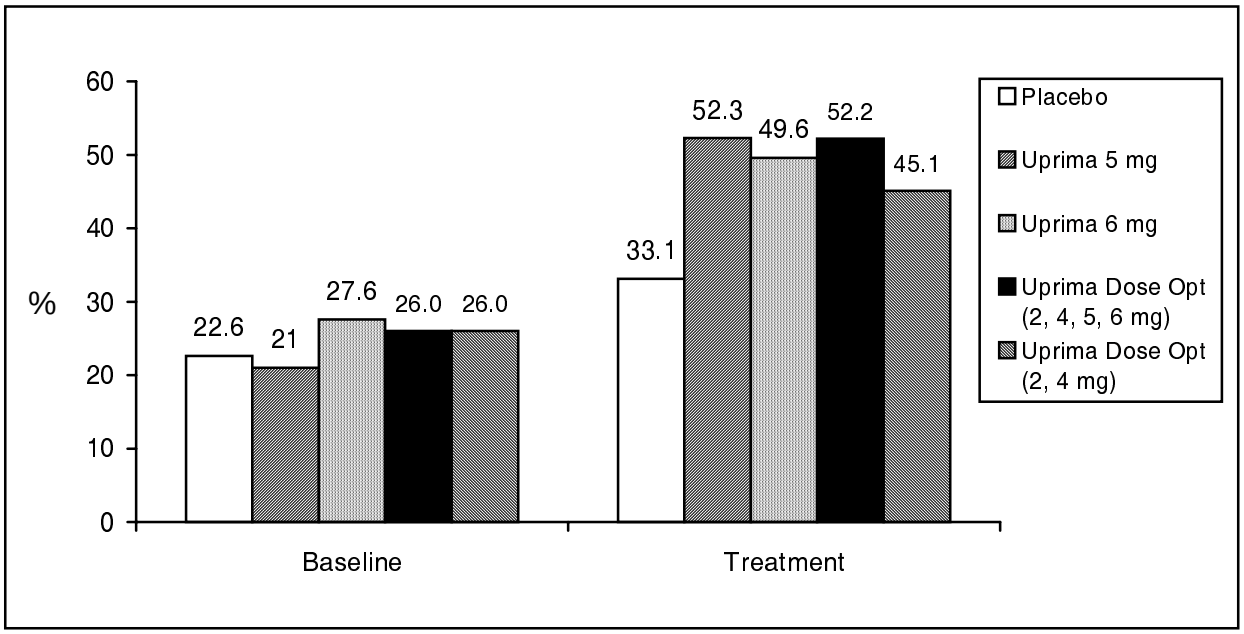
Percentage of Patients Classified as a Treatment "Success"

A patient was classified as a "success" for a certain treatment if at least 50% of his last eight attempts made with the treatment resulted in erections firm enough for intercourse. For both patient and partner assessments, the results of the analysis of percentage of patients classified as a treatment "success" based on the last eight attempts yielded a statistically significantly greater proportion of successful patients in each of the three Uprima treatment groups (54 to 60%) than in the placebo group (39%) with p-values ≤ 0.030. In addition, a similar analysis of the Uprima dose-optimization group versus placebo was performed including only those attempts for patients while they were on 2 or 4 mg. For this analysis, the Uprima group had a statistically significantly higher mean percentage of treatment successes compared to the placebo group (p-value ≤0.011).

Percentage of Attempts Resulting in Intercourse

The results of the analysis of the mean percentage of the last eight attempts resulting in intercourse yielded a statistically significantly greater percentage for all three Uprima treatments (50% to 52%) than for placebo (33%) with p-values ≤0.003. Results from the partner assessments were similar (p-values ≤0.009). In addition, a similar analysis of the Uprima dose-optimization group versus placebo was performed including only those attempts for patients while they were on 2 or 4 mg. For this analysis, the Uprima group had a statistically significantly higher mean percentage of attempts that resulted in intercourse (45%) compared to the placebo group (p-value ≤0.017). These results can be seen in Figure 18.

Figure 18. Average Percentage of Attempts Resulting in Intercourse (Based on Last Eight Attempts) – Patient Data (Study M97-763)



Additional endpoints collected during the study, including data on duration and time to erection, treatment satisfaction, and IIEF questionnaires, support the results of the home-use questionnaires. Partner data (including a partner BSFI) were also collected in this study and were very similar to the patient data. Therefore, they are not provided in detail in this summary.

These results indicate that Uprima 5 and 6 mg fixed doses as well as voluntary dose-optimization with Uprima (whether using 2, 4, 5 and 6 mg or the recommended dosing regimen of 2 and 4 mg) are effective treatments for erectile dysfunction.

8.4.2 Study M97-804: A Phase III Safety Study of Two Fixed Doses of Uprima Tablets versus Placebo in the Treatment of Male Erectile Dysfunction in Patients with Controlled Diabetes

The Phase III diabetic study (M97-804) had the same design as the Phase III crossover studies discussed previously, but included only the 4 and 5 mg doses. The inclusion criteria required patients to have controlled type I or II diabetes as evidenced by glycosylated hemoglobin of <10% and no episodes of ketoacidosis within the past year. Nineteen percent (19%) of patients enrolled in this study had Type I diabetes and 81% of patients had Type II diabetes, both of which were evenly distributed amongst the 4 and 5 mg dose groups. Based on the results from other clinical studies in diabetic patients with ED,[7] the magnitude of the effect of Uprima was expected to be lower than that seen in the general ED population. Moreover, the lower baseline efficacy values observed in the study compared to previous Uprima trials are indicative of more severe ED in this patient population.

In general, baseline and demographic characteristics were similar between dosing groups. However, as shown in Table 21, the IIEF severity of baseline ED was different between the two dosing arms. Patients in the Uprima 4 mg dosing arm had significantly more severe disease (ED) at baseline than did patients in the 5 mg arm (p=0.001). Since it is unknown which (if either) of the two sets of patients is the more representative of the diabetic population, analyses based on both dosing arms combined were performed, in addition to the separate analyses of 4 mg and 5 mg dose.

Table 21. Baseline Erectile Dysfunction Severity (IIEF)/All Randomized Patients Included in the Primary Efficacy Analysis (Study M97-804)

	Uprima (N%)		
Erectile Dysfunction	**5 mg (N=86)**	**4 mg (N=90)**	**Combined (N=176)**
Severe	35 (40.7)	55 (61.1)	90 (51.1)
Moderate	18 (20.9)	13 (14.4)	31 (17.6)
Mild	15 (17.4)	4 (4.4)	19 (10.8)
No Erectile Dysfunction	0 (0.0)	0 (0.0)	0 (0.0)
Unevaluable	18 (20.9)	18 (20.0)	36 (20.5)

Percentage of Attempts with Erection Firm Enough for Intercourse (Primary Efficacy Endpoint)

The results of the analysis of the proportion of all attempts resulting in an erection firm enough for intercourse showed numerical advantages for both dose levels of Uprima over their corresponding placebo doses (based on both patient and partner assessments). These differences were statistically significant for the Uprima 4 mg dose. The results are shown in Table 22 and Figure 19.

Table 22. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse (Study M97-804)

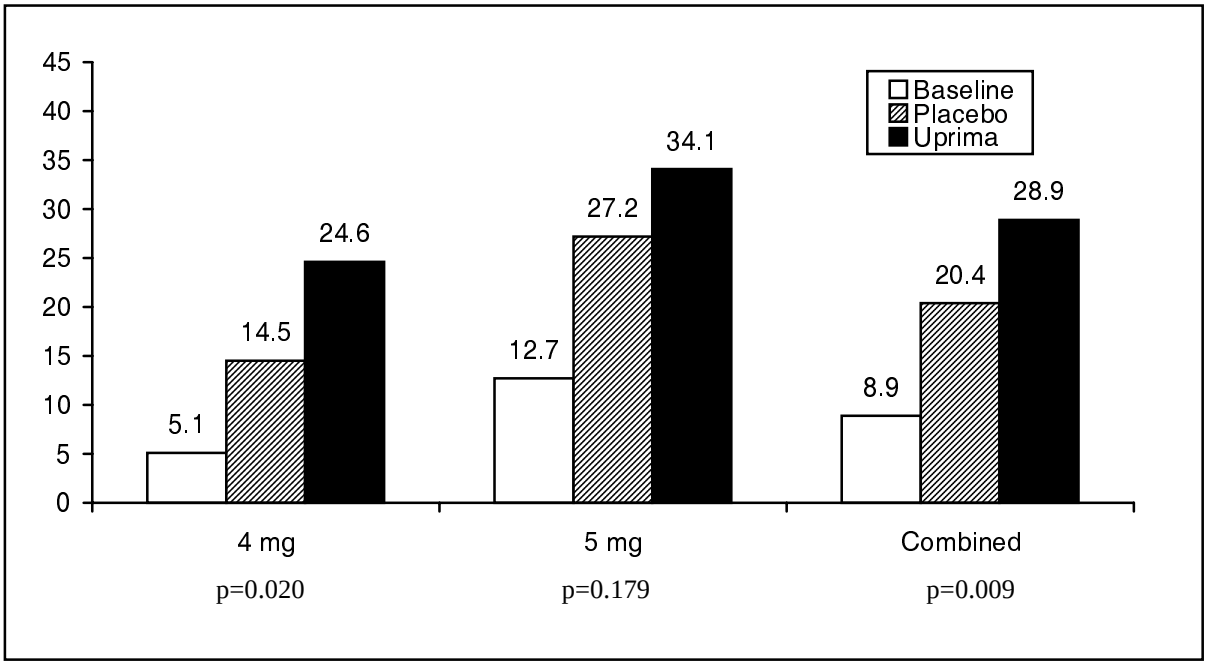
			Placebo		Uprima		Uprima vs. Placebo
Rater	**Dose**	**(N)**	**Success/ Attempts[@]**	**Percent**	**Success/ Attempts[@]**	**Percent**	**p-value**
Patient	4 mg	(90)	115/794	14.5	199/808	24.6	0.020*
	5 mg	(86)	190/699	27.2	224/657	34.1	0.179
	Combined	(176)	305/1493	20.4	423/1465	28.9	0.009**
Partner	4 mg	(82)	99/686	14.4	172/715	24.1	0.015*
	5 mg	(82)	189/677	27.3	212/606	35.0	0.134
	Combined	(164)	283/1362	20.8	384/1321	29.1	0.006**

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively

[@] An attempt is defined as the taking of study drug and completion of a home-use questionnaire.

Note: Although percentages of all attempts are shown, p-values come from an analysis adjusting for individual patient.

Figure 19. Percentage of Attempts Resulting in an Erection Firm Enough for Intercourse – Patient Data (Study M97-804)



Percentage of Attempts Resulting in Intercourse

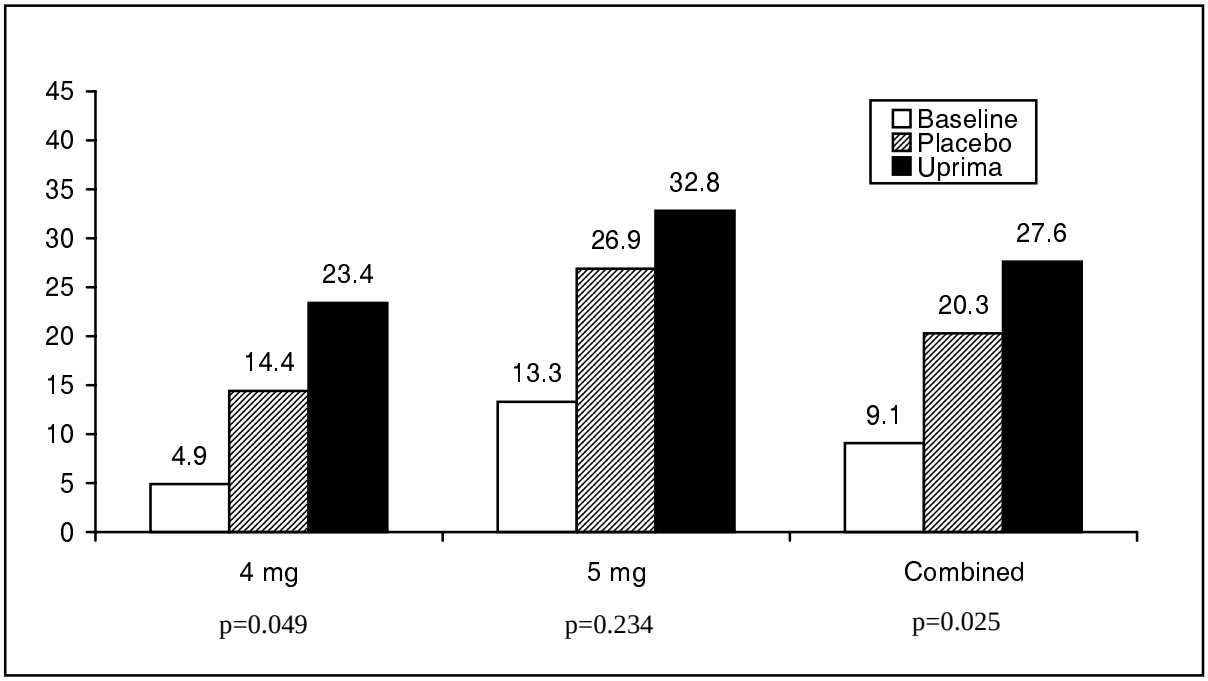
The results of the analysis of proportion of all attempts resulting in intercourse yielded a numerically greater proportion for both of the Uprima doses than for placebo. These differences were statistically significant for the 4 mg doses as well as for both doses combined. These results can be seen in Table 23 and Figure 20.

Table 23. Percentage of Attempts Resulting in Intercourse (Based on All Attempts) (Study M97-804)

			Placebo		Uprima		Uprima vs. Placebo p-value
Rater	Dose	(N)	Success/ Attempts[@]	Percent	Success/ Attempts[@]	Percent	
Patient	4 mg	(90)	114/792	14.4	189/806	23.4	0.049*
	5 mg	(86)	188/699	26.9	212/647	32.8	0.234
	Combined	(176)	302/1491	20.3	401/1453	27.6	0.025*
Partner	4 mg	(82)	102/682	15.0	173/709	24.4	0.021*
	5 mg	(82)	176/671	26.2	213/605	35.2	0.082
	Combined	(164)	278/1353	20.5	386/1314	29.4	0.005**

***, **, * Statistically significant at the p=0.001, 0.01, and 0.05 levels, respectively
[@] An attempt is defined as the taking of study drug and completion of a home-use questionnaire.
Note: Although percentages of all attempts are shown, p-values come from an analysis adjusting for individual patient.

Figure 20. Percentage of Attempts Resulting in Intercourse – Patient Data (Study M97-804)



The fact that the Uprima 4 mg dose level frequently reached statistical significance while the 5 mg dose level did not was possibly attributable to the different patient characteristics in the two dosing groups. Patients within the Uprima 4 mg dosing group

were on the average statistically significantly less likely to have an erection firm enough for intercourse during the lead-in period (baseline) than patients within the 5 mg dosing group. The 5 mg group also had a statistically significantly lower proportion of patients with severe erectile dysfunction than the 4 mg dosing group, perhaps explaining the higher placebo response in the 5 mg group. Since it is unknown which (if either) of the two sets of patients is the more representative of the diabetic population, analyses based on both dosing arms combined were performed, in addition to the separate analyses of 4 mg and 5 mg dose.

When both Uprima dosing arms were combined, a statistically significantly greater proportion of attempts resulting in an erection firm enough for intercourse based on patient assessment were noted for Uprima versus placebo, with 29% of all attempts on Uprima resulting in an erection firm enough for intercourse (versus 20% on placebo). Similarly, a statistically significantly larger proportion of attempts resulted in intercourse based on patient assessment for Uprima dosing versus placebo dosing (28% versus 20%). It should be noted that this population had lower baseline scores (5-13%) for both erections firm enough for intercourse and attempts resulting in intercourse than the general ED population studied. Statistically significant improvements in mean IIEF and BSFI indices were also seen.

This suggests that Uprima is an effective treatment for erectile dysfunction in diabetic patients.

8.5 Open-Label Short-Term Study

8.5.1 Study M98-876: A Phase III At Home Use Study Evaluating the Efficacy and Safety of Escalating Doses of Uprima 2, 4 and 5 mg in the Treatment of Male Erectile Dysfunction

The Phase III dose-at-home study (M98-876) was an open-label, dose-optimization study. All doses were taken at home (previous studies had first dose administered in the office

as discussed in more detail Section 9.1.7). Instructions for the proper administration of study drug as well as written instructions regarding prodomal vasovagal symptoms associated with syncope (similar to proposed Patient Package Insert, see Appendix E) were given to all patients at the beginning of the study. All patients were initially dispensed Uprima 2 mg and dosed at home. During the next three weeks of treatment, the optimal dose of Uprima (2, 4 or 5 mg) was determined. During the last four weeks of treatment, patients continued on the optimal dose determined during the first three weeks of treatment. The entire study duration was 9-11 weeks, which included a 2-4 week screening period.

One hundred fifty-one (151) patients with erectile dysfunction were enrolled in this study. Entrance criteria in this study were less restrictive than previous studies, as NPT testing at baseline was not required and heavy smokers were included. As a result, almost 80% of patients had moderate to severe ED based on IIEF at baseline. In addition, a number of patients with organic disease were enrolled, including 38% with hypertension, 18% with diabetes, 23% with coronary artery disease, and 27% with BPH. Although this study was designed primarily to examine safety, efficacy was also assessed.

For all efficacy variables, patients demonstrated improvement from baseline following the use of Uprima tablets (2, 4 and 5 mg). At baseline, patients reported that, on the average, 13.7% of all attempts resulted in erections firm enough for intercourse. These baseline rates are noticeably lower than those seen in previous studies, probably due to the less restrictive entry criteria which resulted in patients with more severe ED. During at home use of Uprima, the average percentage of each patient's last 8 attempts which resulted in erections firm enough for intercourse across patients was 39.8%. The average percentage of attempts resulting in intercourse across patients was 40.8% overall based on each patients' last 8 attempts versus 13.0% at baseline.

The mean changes from baseline in IIEF indices indicated a statistically significant increase (improvement) in all indices at both Week 3 and Week 7 except for the index of sexual desire.

8.6 Supportive Open-Label Long-Term Studies

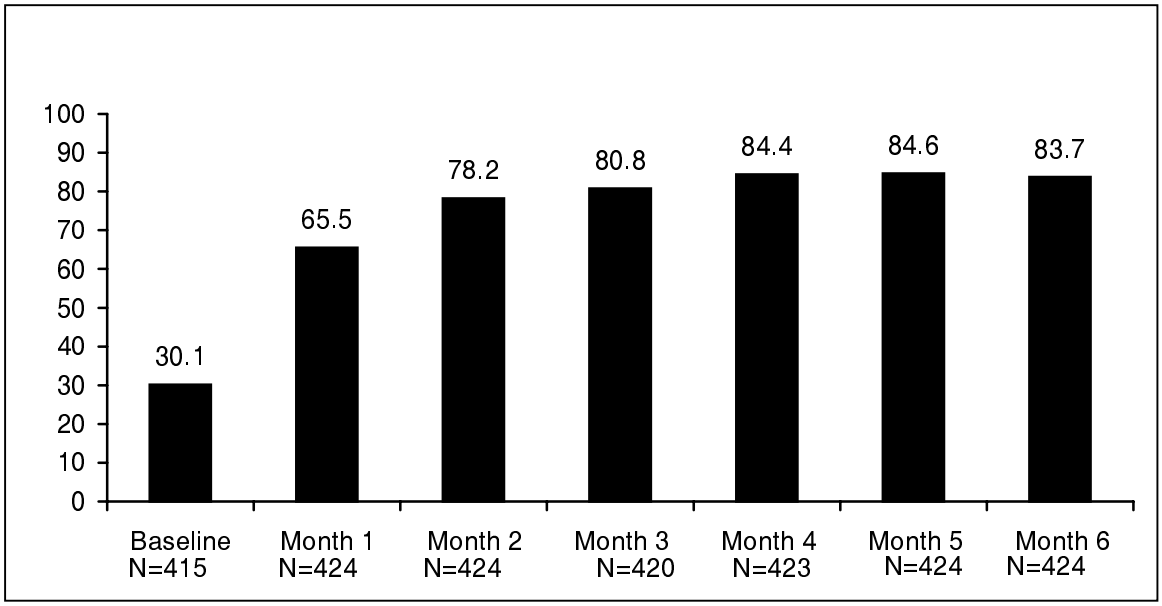
Five uncontrolled, long-term studies were conducted primarily to evaluate the long-term safety of Uprima. The first long-term study (M96-471) was a Phase III, open-label, flexible-dose, efficacy and safety follow-up study for M96-470 using 2, 4 and 6 mg Uprima. The duration was 6 months. The second long-term study (M97-659) was a Phase III, open-label, flexible-dose, efficacy and safety follow-up study for M97-658 using 2, 4, 5 and 6 mg Uprima. The duration was 6 months. The third long-term study (M97-682) is a Phase III, open-label, flexible-dose safety extension study using 2, 4, 5 or 6 mg Uprima. The duration of this study is 3 years, and the study is ongoing. The fourth Long-Term Study (M97-793) is a Phase III, open-label, flexible dose safety extension study for special population patients from the post-radical prostatectomy and diabetes short-term studies using 2, 4, 5 or 6 mg Uprima. The duration of the study is two years, and the study is ongoing. The fifth long-term study M98-936 was a Phase III, open-label, flexible-dose safety extension study using 2, 4, 5 or 6 mg Uprima. The duration of this study is two years, and the study is ongoing. Interim data from the ongoing long-term studies were submitted in the NDA.

Patient satisfaction with Uprima was evidenced by the high level of enrollment in the long-term studies. Eighty-five percent (85%) of eligible patients continued into one of the long-term, open-label studies.

Data from the long-term studies provide evidence that Uprima efficacy is maintained over time. For the 127 patients with total exposure to Uprima over 1 year, the average percentage of attempts after a year resulting in an erection firm enough for intercourse

was 84.6%. In addition, the percentage of erections firm enough for intercourse in patients who remained in a long-term study for at least six months demonstrated a similar trend, as shown in Figure 21.

Figure 21. Percentage of Erections Firm Enough for Intercourse (Long-Term Studies M96-471, M97-659, and M97-682) All Doses



8.7 Overall Efficacy Conclusions

The results of each of the studies included in this summary are consistent and clearly demonstrate that Uprima is an efficacious treatment for patients with erectile dysfunction.

In the four Phase III general population studies (M96-470, M97-658, M98-941 and M97-763), all dosage levels of Uprima resulted in statistically and clinically significant differences from placebo in the proportion of attempts which resulted in an erection firm enough for intercourse as well as the number of attempts which resulted in intercourse. Statistically and clinically significant increases in the satisfaction with each attempt were also noted in these studies. The results from the analyses of validated patient

questionnaires yielded statistically and clinically significant improvements for each dose in each of these studies. Patient improvements were also substantiated by partner evaluations which consistently mirrored the results of the corresponding patient analyses.

Although a dose-response was noted with respect to efficacy, there appears to be little therapeutic gain beyond the 4 mg dose. Both the 2 and 4 mg doses consistently demonstrate statistically significant improvements over placebo for both patient and partner assessments of primary and secondary endpoints as well as in important subgroups of patients.

These results indicate that Uprima is an efficacious treatment for patients with erectile dysfunction.

8.8 References

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9.0 Summary of the Safety of Uprima in the Treatment of Erectile Dysfunction

Overall, 2379 patients have received at least one dose of Uprima in Phase II/III studies and took a total of 73,736 doses. An additional 656 subjects received at least one dose of Uprima in Phase I studies. The adverse event section that follows focuses primarily on the Phase II/III studies, although subjects in the Phase I studies exhibited a similar safety profile and are included in the discussions of serious adverse events, syncope, vital signs, and Holter monitor results.

9.1 Adverse Events

Treatment-emergent adverse events are defined as all adverse events reported to TAP on adverse event case report forms which occur during or after the first dose or within seven days of last dose regardless of relationship to study drug (active or placebo) or treatment group. Related treatment-emergent adverse events are all treatment-emergent adverse events classified by the investigators conducting the studies to be definitely, probably, possibly related to or of unknown relationship to study drug. Thus, treatment-related adverse events only exclude adverse events considered not related to study drug by the investigator.

Eleven Phase II/III studies have been completed and analyzed. Three additional open-label, long-term, Phase III safety studies underwent interim analysis for the NDA and 4-Month Safety Update and these results are presented in this section. Related treatment-emergent adverse events for all doses of Uprima are presented in the section for the combined analysis of the Phase II/III studies. In addition, the incidence of related treatment-emergent adverse events for recommended doses (Uprima 2 and 4 mg) are summarized separately and presented in this section. Each patient who participated both in the Phase II/III short-term and one or more of the long-term follow-up studies was treated as one patient for these summaries.

Unless otherwise noted, all adverse event summaries are on a per patient basis; that is, any patient with one or more episodes of an adverse event are included. For a prn drug, the incidence per administration may be considered more appropriate and these rates would obviously be much lower than those summarized on a per patient basis. Nausea was the most frequently reported adverse event and syncope, although uncommon, was the most clinically significant.

9.1.1 Phase II/III Studies-All Doses

Of the 2379 patients who received at least one dose of Uprima in Phase II/III trials, 1649 (69.3%) experienced at least one adverse event regardless of relationship to study drug. A total of 1274 patients (53.6%) reported treatment-emergent adverse events that were deemed possibly, probably, or definitely related or of unknown relationship to Uprima.

Table 24 presents the most frequently reported (≥ 5% incidence) related treatment-emergent adverse events while receiving Uprima (including higher than recommended doses).

Table 24. Related Treatment-Emergent Adverse Events Reported by ≥ 5% of Uprima Patients (2, 4, 5 and 6 mg) in the Phase II/III Studies

COSTART Term	Adverse Events N=2379 n (%)
Nausea	756 (31.8)
Dizziness	423 (17.8)
Sweating	334 (14.0)
Somnolence	320 (13.5)
Yawning	262 (11.0)
Vomiting	195 (8.2)
Headache	189 (7.9)
Asthenia	149 (6.3)
Vasodilatation	140 (5.9)

For all Phase II/III studies combined, nausea was the most frequently reported Uprima (2, 4, 5 or 6 mg) related treatment-emergent adverse event followed in incidence by dizziness, sweating, somnolence, and yawning. Nausea, dizziness and sweating are considered to be vasovagal adverse events, as are pallor, vomiting, and vasodilatation. The majority of nausea episodes reported during the study were mild in severity. Only 1.3% of patients reported severe nausea related to Uprima.

The majority of related treatment-emergent adverse events were mild or moderate in severity. Only 75 of 2379 patients (3.2%) reported a severe event related to Uprima. There were no reports of priapism at any of the doses studied (2, 4, 5 or 6 mg).

9.1.2 Phase II/III Studies- Uprima 2 and 4 mg

After an extensive review of all Phase III clinical data, a decision was made not to pursue marketing of the 5 mg and 6 mg doses of Uprima. All doses of Uprima (2, 4, 5 and 6 mg) have been proven to be efficacious for treating erectile dysfunction based on patient and partner assessments in multiple controlled clinical trials. However, little therapeutic gain has been demonstrated at doses above 4 mg. Higher doses (5 and 6 mg) are associated with an increased frequency of adverse events. Despite the absence of overwhelming safety issues, the 5 and 6 mg doses will not be recommended for dosing, thus providing a greater safety margin for the use of Uprima.

The Uprima 2 and 4 mg doses provide a significant improvement in safety profile relative to all doses, reducing the incidence of related treatment-emergent adverse events to 34.6% compared to 53.6% for all doses combined.

The following table presents the most frequently reported ($\geq$5% incidence) related treatment-emergent adverse events for the 2 and 4 mg doses combined.

Replace page 87

Table 25. Related Treatment-Emergent Adverse Events Reported by ≥ 5% of Uprima (2 and 4 mg) Patients in the Phase II/III Studies

COSTART Term	Adverse Events N=1925 n (%)
Nausea	298 (15.5)
Dizziness	180 (9.4)
Somnolence	155 (8.1)
Yawning	117 (6.1)
Sweating	111 (5.8)
Headache	102 (5.3)

Nausea and dizziness were the most frequently reported related treatment-emergent adverse events experienced by patients treated with 2 or 4 mg Uprima, although the rates are lower (15.5 % and 9.4%, respectively) than those observed for all doses (31.8% and 17.8%, respectively). Only 0.4% of patients reported severe nausea. The substantially lower incidence of related treatment-emergent adverse events among patients treated with 2 or 4 mg Uprima compared to those treated with 2, 4, 5 or 6 mg doses combined is clinically relevant.

The vast majority of treatment-emergent adverse events were mild or moderate, and reports of severe related treatment-emergent adverse events were infrequent (1.4 % of patients). Comparatively, when all doses (2, 4, 5 and 6 mg) of Uprima are combined, a higher percentage of patients reported severe related treatment-emergent adverse events (3.2% of patients).

For a prn drug, the incidence of adverse events per administration of study drug is also of interest. Therefore, the percentages of Uprima administrations resulting in specific adverse events were also calculated. Only 2.2% of the more than 35,000 Uprima 2 or 4 mg administrations resulted in nausea, and only 0.2% of these administrations led to vomiting.

corrected sentence

9.1.3 Adverse Events for Subgroups in the Phase II/III Studies – All Doses (2, 4, 5 and 6 mg)

Safety data were summarized for the combined Phase II/III studies by nine subgroups: weight, age, race, smoking status, alcohol use, diabetic status, hypertensive status, coronary artery disease status and benign prostatic hyperplasia (BPH) status.

Although there were a few statistically significant differences in adverse events within each subgroup analysis, they were neither consistent nor clinically significant. In general, it was noted that smokers experienced a lower percentage of adverse events than did non/ex-smokers. In addition, diabetic and hypertensive patients reported fewer adverse events than did non-diabetics and non-hypertensives, respectively. Adverse event rates were similar regardless of coronary artery disease status or BPH status. In addition, adverse events did not increase with increasing age. Adverse event rates were also similar among subgroups for weight, age, race, and alcohol use.

The adverse event subgroup analyses are summarized in Table 26.

Table 26. Related Treatment-Emergent Adverse Events Reported by ≥ 5% of Patients by Subgroups in the Phase II/III Studies (All Doses)

COSTART Term	Hypertension n (%)		Diabetes n (%)		CAD n (%)	
	Yes N=717	No N=1604	Yes N=367	No N=1954	Yes N=368	No N=1953
Nausea	189 (26.4)	535 (33.4)	81 (22.1)	643 (32.9)	112 (30.4)	612 (31.3)
Dizziness	101 (14.1)	301 (18.8)	38 (10.4)	364 (18.6)	68 (18.5)	334 (17.1)
Sweating	80 (11.2)	235 (14.7)	32 (8.7)	283 (14.5)	50 (13.6)	265 (13.6)
Somnolence	94 (13.1)	219 (13.7)	38 (10.4)	275 (14.1)	61 (16.6)	252 (12.9)
Yawning	82 (11.4)	161 (10.0)	22 (6.0)	221 (11.3)	31 (8.4)	212 (10.9)
Vomiting	47 (6.6)	140 (8.7)	19 (5.2)	168 (8.6)	33 (9.0)	154 (7.9)
Headache	49 (6.8)	136 (8.5)	16 (4.4)	169 (8.6)	35 (9.5)	150 (7.7)
Asthenia	33 (4.6)	94 (5.9)	11 (3.0)	116 (5.9)	26 (7.1)	101 (5.2)
Vasodilation	35 (4.9)	102 (6.4)	9 (2.5)	128 (6.6)	22 (6.0)	115 (5.9)
Taste Perversion	39 (5.4)	77 (4.8)	3 (0.8)	113 (5.8)	19 (5.2)	97 (5.0)

Table 26. Related Treatment-Emergent Adverse Events Reported by ≥ 5% of Patients by Subgroups in the Phase II/III Studies (All Doses) (Cont.)

COSTART Term	BPH n (%)		Alcohol Use n (%)		Smoking n (%)	
	Yes N=361	No N=1960	Yes N=1474	No N=858	Yes N=363	No N=1968
Nausea	122 (33.8)	602 (30.7)	467 (31.7)	261 (30.4)	59 (16.3)	669 (34.0)
Dizziness	71 (19.7)	331 (16.9)	265 (18.0)	137 (16.0)	33 (9.1)	369 (18.8)
Sweating	55 (15.2)	260 (13.3)	212 (14.4)	101 (11.8)	27 (7.4)	286 (14.5)
Somnolence	43 (11.9)	270 (13.8)	200 (13.6)	115 (13.4)	11 (3.0)	304 (15.4)
Yawning	32 (8.9)	211 (10.8)	166 (11.3)	77 (9.0)	27 (7.4)	216 (11.0)
Vomiting	26 (7.2)	161 (8.2)	112 (7.6)	75 (8.7)	9 (2.5)	178 (9.0)
Headache	31 (8.6)	154 (7.9)	109 (7.4)	76 (8.9)	18 (5.0)	167 (8.5)
Asthenia	22 (6.1)	105 (5.4)	93 (6.3)	46 (5.4)	9 (2.5)	130 (6.6)
Vasodilation	20 (5.5)	117 (6.0)	80 (5.4)	47 (5.5)	11 (3.0)	116 (5.9)
Taste Perversion	18 (5.0)	98 (5.0)	73 (5.0)	43 (5.0)	17 (4.7)	99 (5.0)

Table 26. Related Treatment-Emergent Adverse Events Reported by ≥ 5% of Patients by Weight, Age, Race in the Phase II/III Studies (All Doses) (Cont.)

COSTART Term	Weight (lbs.) n (%)		
	<180 N=648	180-210 N=968	>210 N=760
Nausea	238 (36.7)	311 (32.1)	207 (27.2)
Dizziness	121 (18.7)	179 (18.5)	123 (16.2)
Sweating	108 (16.7)	138 (14.3)	88 (11.6)
Somnolence	98 (15.1)	118 (12.2)	104 (13.7)
Yawning	71 (11.0)	106 (11.0)	85 (11.2)
Vomiting	83 (12.8)	73 (7.5)	39 (5.1)
Headache	57 (8.8)	71 (7.3)	61 (8.0)
Asthenia	55 (8.5)	55 (5.7)	39 (5.1)
Vasodilation	39 (6.0)	57 (5.9)	44 (5.8)
Taste Perversion	30 (4.6)	44 (4.5)	42 (5.5)

Table 26. Related Treatment-Emergent Adverse Events Reported by ≥ 5% of Patients by Weight, Age, Race in the Phase II/III Studies (All Doses) (Cont.)

COSTART Term	Age n (%)			
	<46 N=353	46-55 N=820	56-65 N=875	>65 N=331
Nausea	115 (32.6)	260 (31.7)	280 (32.0)	101 (30.5)
Dizziness	54 (15.3)	141 (17.2)	157 (17.9)	71 (21.5)
Sweating	37 (10.5)	108 (13.2)	130 (14.9)	59 (17.8)
Somnolence	38 (10.8)	116 (14.1)	128 (14.6)	38 (11.5)
Yawning	41 (11.6)	85 (10.4)	100 (11.4)	36 (10.9)
Vomiting	31 (8.8)	60 (7.3)	70 (8.0)	34 (10.3)
Headache	32 (9.1)	65 (7.9)	64 (7.3)	28 (8.5)
Asthenia	21 (5.9)	53 (6.5)	51 (5.8)	24 (7.3)
Vasodilation	22 (6.2)	45 (5.5)	46 (5.3)	27 (8.2)
Pallor	11 (3.1)	30 (3.7)	26 (3.0)	17 (5.1)
Taste Perversion	10 (2.8)	45 (5.5)	48 (5.5)	14 (4.2)

COSTART Term	Race n (%)	
	Caucasian N=2107	Non-caucasian N=272
Nausea	697 (33.1)	59 (21.7)
Dizziness	380 (18.0)	43 (15.8)
Sweating	313 (14.9)	21 (7.7)
Somnolence	278 (13.2)	42 (15.4)
Yawning	236 (11.2)	26 (9.6)
Vomiting	174 (8.3)	21 (7.7)
Headache	170 (8.1)	19 (7.0)
Asthenia	138 (6.5)	11 (4.0)
Vasodilation	130 (6.2)	10 (3.7)
Taste Perversion	99 (4.7)	18 (6.6)

The subgroup analyses indicate that Uprima did not result in an increase in frequency of adverse events in these important subgroups of patients.

9.1.4 Adverse Events: Phase III Crossover (M96-470, M97-658 and M98-941) and Parallel (M97-763) Studies

In the Phase III Crossover studies, dose response relationships could be examined. The 2 and 4 mg doses produced lower overall incidences of Uprima related adverse events (16.6% and 39.2%, respectively) compared to 5 mg (52.8%) and 6 mg (60.7%). The

incidence of the most common Uprima related treatment-emergent adverse events, including nausea and dizziness, increased in frequency with increased dose. The majority of related treatment-emergent adverse events were mild to moderate in severity. Adverse events that occurred in $\geq$ 5% of patients in the Phase III crossover studies are summarized in Table 27.

Table 27. Related Treatment-Emergent Adverse Events Reported by ≥ 5% of Patients in the Phase III Crossover Studies (M96-470, M97-658 and M98-941)

COSTART Term	2 mg Group		4 mg Group		5 mg Group		6 mg Group	
	Placebo N=436 n (%)	Uprima N=429 n (%)	Placebo N=414 n (%)	Uprima N=426 n (%)	Placebo N=263 n (%)	Uprima N=282 n (%)	Placebo N=236 n (%)	Uprima N=262 n (%)
Nausea	5 (1.2)	9 (2.1)	8 (1.9)	87 (20.4)	6 (2.3)	87 (30.9)	4 (1.7)	103 (39.3)
Dizziness	13 (3.0)	13 (3.0)	8 (1.9)	59 (13.9)	7 (2.7)	57 (20.2)	1 (0.4)	52 (19.9)
Sweating	0 (0.0)	7 (1.6)	0 (0.0)	42 (9.9)	0 (0.0)	45 (16.0)	3 (1.3)	53 (20.2)
Somnolence	7 (1.6)	9 (2.1)	3 (0.7)	45 (10.6)	2 (0.8)	33 (11.7)	1 (0.4)	37 (14.1)
Yawning	2 (0.5)	13 (3.0)	2 (0.5)	36 (8.5)	4 (1.5)	37 (13.1)	1 (0.4)	29 (11.1)
Asthenia	0 (0.0)	4 (0.9)	1 (0.2)	18 (4.2)	1 (0.4)	11 (3.9)	1 (0.4)	27 (10.3)
Vomiting	0 (0.0)	3 (0.7)	0 (0.0)	11 (2.6)	0 (0.0)	24 (8.5)	0 (0.0)	29 (11.1)
Headache	10 (2.3)	15 (3.5)	10 (2.4)	22 (5.2)	9 (3.4)	13 (4.6)	4 (1.7)	18 (6.9)
Taste Perversion	3 (0.7)	12 (2.8)	2 (0.5)	28 (6.6)	2 (0.8)	19 (6.7)	5 (2.1)	19 (7.3)
Vasodilatation	4 (0.9)	4 (0.9)	1 (0.2)	12 (2.8)	2 (0.8)	18 (6.4)	2 (0.9)	26 (9.9)
Pallor	0 (0.0)	1 (0.2)	0 (0.0)	9 (2.1)	0 (0.0)	19 (6.7)	0 (0.0)	8 (3.1)

The results of the Phase III parallel study (M97-763) showed that the dose-optimization group produced the lowest overall incidence of related treatment-emergent adverse events (54.5%) compared with the 5 mg fixed dose (62.2%) and 6 mg (68.5%) fixed dose, despite the fact that 78% of patients optimized to the 5 or 6 mg dose. The majority of related treatment-emergent adverse events were mild to moderate in severity. Reports of severe adverse events were infrequent, occurring in 1.7% of patients treated with Uprima 5 mg fixed dose, 5.6% of Uprima 6 mg fixed dose patients and 3.7% of the dose-optimization group.

Evidence that patients accommodate to adverse events with Uprima is seen in the decrease in percentages of adverse events as patients moved from the dose-optimization period to the maintenance period. Table 28 summarizes treatment-emergent adverse events reported by all patients who were in both the dose-optimization period and the maintenance periods (last 4 weeks). The incidence of nausea decreased substantially for all of the Uprima groups, ranging from 25% to 44% during the dose-optimization period as compared to 12% to 17% during the maintenance period.

Table 28. Most Common Treatment-Emergent Adverse Events Reported by All Patients Who Were in Both the Dose-Optimization and Maintenance Periods in the Phase III Parallel Study (M97-763)

Adverse Event	Placebo N=105 n (%)	Uprima 5 mg fixed N=94 n (%)	Uprima 6 mg fixed N=70 n (%)	Uprima Dose-Optimiztion (2, 4, 5 and 6 mg) N=197 n (%)
Dose-Optimization Period				
Nausea	3 (2.9)	32 (34.0)	31 (44.3)	49 (24.9)
Headache	10 (9.5)	11 (11.7)	13 (18.6)	31 (15.7)
Dizziness	0 (0.0)	13 (13.8)	11 (15.7)	22 (11.2)
Sweating	1 (1.0)	9 (9.6)	11 (15.7)	20 (10.2)
Yawning	6 (5.7)	13 (13.8)	11 (15.7)	19 (9.6)
Somnolence	2 (1.9)	14 (14.9)	8 (11.4)	14 (7.1)
Maintenance Period				
Nausea	0 (0.0)	11 (11.7)	12 (17.1)	24 (12.2)
Headache	4 (3.8)	2 (2.1)	4 (5.7)	11 (5.6)
Dizziness	0 (0.0)	4 (4.3)	4 (5.7)	8 (4.1)
Sweating	0 (0.0)	0 (0.0)	1 (1.4)	9 (4.6)
Yawning	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.0)
Somnolence	1 (1.0)	4 (4.3)	0 (0.0)	4 (2.0)

9.1.5 Adverse Events: Phase III Long-Term Studies (M96-471, M97-659, M98-936, M97-682/Extended Long-Term, and M97-793/Special Population Long-Term)

Five long-term, Phase III studies to assess safety are presented in this section. Two of the studies (M96-471/first extension and M97-659/second extension) have been completed. The third extension study (M98-936) and the extended long-term study (M97-682) are ongoing and will be completed in 3rd quarter 2001. The special population long-term study (M97-793) is also underway and will be completed in the year 2002.

Of the related treatment-emergent adverse events reported for the long-term studies (M96-471, M97-659, M97-682, M98-936 and M97-793), the majority were mild or moderate in severity; severe adverse events were rarely reported (1.9% of patients).

Nausea was the most commonly reported adverse event for all five studies. Table 29 lists the most frequently (≥ 5% incidence) reported related treatment-emergent adverse events in the Phase III long-term studies.

Table 29. Related Treatment–Emergent Adverse Events Reported by ≥ 5% of Uprima (2, 4, 5, 6 mg) Patients in the Phase III Long-Term, Extended Long-Term, and Special Population Long-Term Studies

COSTART Term	Long-Term Studies (Six-Months) * N = 687 Uprima n (%)	Special Population Long-Term Study (Two Years, Ongoing) N = 115 Uprima n (%)	Extended Long-Term Study (Three years, Ongoing) N = 483 Uprima n (%)
Nausea	178 (25.9)	18 (15.7)	103 (21.3)
Somnolence	86 (12.5)	8 (7.0)	37 (7.7)
Dizziness	88 (12.8)	7 (6.1)	48 (9.9)
Sweating	68 (9.9)	8 (7.0)	39 (8.1)
Vomiting	45 (6.6)	4 (3.5)	26 (5.4)
Yawning	49 (7.1)	4 (3.5)	28 (5.8)
Headache	26 (3.6)	4 (3.5)	27 (5.6)

* Includes an ongoing 2 year study (M98-936) in which no patient had been active for more than 6 months at the time of the interim analysis.

9.1.6 Serious Adverse Events (SAEs)

As defined by ICH Guidelines, a serious adverse event is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or 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 appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. The protocols for the Phase III crossover study M96-470 and its follow-up (M96-471) included other serious adverse events such as cancer and events that required intervention to prevent impairment/damage.

Table 30 summarizes the incidence of serious adverse events by treatment over all Uprima studies.

Table 30. Overall Incidence of Serious Adverse Events for Patients Treated with Uprima in the Phase I-III Studies

Treatment	Relationship to Study Drug	
	Related SAEs n (%)	Not Related SAEs n (%)
Uprima 2 mg	0 (0.0)	8 (0.3)
Uprima 4 mg	3 (0.1)	13 (0.4)
Uprima 5 mg	9 (0.3)	18 (0.6)
Uprima 6 mg	3 (0.1)	22 (0.7)
TOTAL (N=3035)	15 (0.5)	61 (2.0)

Note: Six patients reported unrelated SAEs while on placebo.

A total of 82 subjects/patients in the 27 studies included in the NDA and 4-Month safety update reported a serious adverse event. Seventy-six (76) subjects/patients reported a serious adverse event following Uprima administration and six reported serious adverse events after receiving placebo.

The majority of serious adverse events were not related to study drug as assessed by the investigator. Only fifteen (15) events were considered by the investigators to be possibly related to Uprima. Twelve of the 15 events occurred while patients were taking Uprima 5 or 6 mg. These included one patient who reported atrial flutter, one patient who experienced arrhythmia, two patients who experienced significant hypotension and eight patients who experienced syncopal events. Only three of the 15 events occurred while patients were taking Uprima 4 mg; all of these patients experienced syncopal events (one patient also experienced an EKG abnormality of borderline first AV-block with non-specific t-wave flattening). No serious adverse events related to study drug were reported in patients taking 2 mg Uprima.

No deaths occurred either during or immediately after any of the studies included in the NDA and the Safety Update. Furthermore, no myocardial infarctions or strokes related to

Uprima were observed during clinical trials. There were, however, three myocardial infarctions and one stroke which were deemed not related to study drug by the investigator.

9.1.7 Syncope

Syncope is defined as a sudden transient loss of consciousness with spontaneous recovery associated with hypotension, bradycardia or both which usually occurs when a person is in the upright position. The most common cause is reflex peripheral vasodilatation (vasovagal episodes) which can be induced by a variety of pharmacologic agents.

With guidance from the FDA, TAP performed significant analyses and exploratory studies to better understand the pathophysiology of syncope reported in these clinical trials. Uprima has the potential to induce hypotension and orthostatic cardiovascular changes secondary to vasovagal events. Evidence from the literature and TAP animal studies[1,2,3,4,5,6] indicates that cardiovascular autonomic homeostasis is modulated by Uprima via dopaminergic activity which may produce hypotension and/or bradycardia in susceptible individuals in association with orthostatic maneuvers. Uprima has been found to exert no effect on cardiac conduction. There is evidence that the pathophysiological mechanism of syncope associated with Uprima is vasovagal and not cardiogenic.

Forty-eight (48) syncopal events were reported in the Phase I-III clinical studies. Forty-one (41) of these events were considered by the investigator to be at least possibly related to study drug, two of which resulted in injury (skull fracture when patient hit his head on the sink; minor injuries secondary to an automobile accident). Seven of these syncopal events were determined not to be related to study drug (one was prior to Uprima dosing but following a blood draw; three occurred 4 or more days after dosing; one diabetic patient experienced marked hypoglycemia with a blood glucose of 15 mg; one patient had a massive GI bleed with hematocrit of 26%; and one patient who had consumed a half a bottle of wine, struck his head and then loss consciousness). Eight of

the 41 Uprima-related syncopal events occurred during Phase I studies and 33 events occurred during Phase II/III studies. Syncopal events on Uprima were nearly always accompanied by a prodrome of one or more of the following vasovagal events: moderate/severe nausea, dizziness, vomiting, sweating, pallor or vasodilatation (further discussion of prodrome is included later in this section).

The overall incidence of syncope in the Phase II/III studies was 1.4% (33/2379). However, the incidence of syncope per administration of Uprima is much lower. The 2379 patients in the Phase II/III studies took a total of 73,736 doses of Uprima and experienced 33 syncopal events; therefore, the overall rate of syncope per administration is 0.04%. These syncopal episodes were more likely to occur with the higher doses of Uprima (5 or 6 mg) and within 60 minutes of dosing. All possibly related syncopes occurred within two hours of dosing (except for one event which occurred 16 hours post-dosing after heavy physical exertion on a hot day which was judged by the investigator to be possibly-related). Patients who experienced syncope and were re-challenged did not experience any serious adverse events or additional syncopal episodes with subsequent dosing.

The distribution of syncopal events across all dose groups shows that the 2 and 4 mg Uprima doses result in a lower incidence of syncope (0.8%) compared to all doses combined (1.4%). In addition, dose-optimization (initial dose of 2 mg with a subsequent increase to 4 mg) resulted in a lower incidence of syncope (0.6%) compared to the incidence for fixed dose administration using 4 mg (1.2%). These data are presented in Table 31.

Table 31. Distribution of Syncopal Events for All Uprima Studies

Uprima Dose	Overall n/N (%)	Fixed Dose n/N (%)	Dose-Optimization n/N (%)
Uprima 2 mg	2/964 (0.2)	2/964 (0.2)@	---
Uprima 4 mg	11/1279 (0.9)	7/590 (1.2)	4/690 (0.6)
Uprima 5 mg	13/1416 (0.9)	7/860 (0.8)	6/556 (1.1)
Uprima 6 mg	15/1252 (1.2)	13/621 (2.1)	2/631 (0.3)
Uprima 8 mg	0/45 (0.0)	---	0/45 (0.0)
Combined: All Doses	41/3035 (1.4)	---	---
Combined: 2 and 4 mg	13/1554 (0.8)	---	---

@ Includes data from patients who took 2 mg as a fixed dose throughout the study as well as patients who took 2 mg and subsequently optimized to a higher dose.

Many of the syncopal events occurred before specific written instructions were developed for patients to explain what to do if prodomal vasovagal symptoms occur. These were developed after most of the Phase III studies were initiated. Prior to these improved instructions, all patients were given their first dose in the office. Similar instructions to those currently proposed in the patient package insert (Appendix E) were used in Study M98-876 where patients took their first dose at home. Only one of 146 patients (0.7%) in that study had a syncopal event, and that patient was on Uprima 5 mg. Subsequently, a large study (863 patients) with these instructions and using the recommended dose level and regimen has been completed and will be submitted to the FDA.

In the Phase II/III studies, 16 of 33 patients who experienced syncope prematurely withdrew from study participation and 17 elected to be re-challenged with Uprima. All patients who were re-challenged continued study participation without further syncopal episodes. In the Phase I studies, three of eight subjects with syncopal episodes related to Uprima prematurely withdrew from study participation and one subject completed the study with that single dose. Four of eight subjects elected to be re-challenged with Uprima and continued the study without any further syncopal episodes. The 21 patients/subjects in the Phase I-III studies who were rechallenged took a total of 605 additional doses of Uprima.

For related syncopal events, the median time to onset of syncope was approximately 35 minutes after Uprima administration with a range of approximately 20 minutes to 120

minutes post-dosing. This is consistent with peak plasma concentration of apomorphine. The median duration of these episodes was approximately 45 seconds and ranged from one second to five minutes.

Overall, the majority of subjects (26 of 41) who experienced treatment-related syncope experienced the event either after their first dose of Uprima or after their first dose at an increased dosage strength (1 of 2 subjects for 2 mg, 8 of 11 subjects for 4 mg, 10 of 13 subjects for 5 mg, and 7 of 15 subjects for 6 mg Uprima). One of the subjects who experienced syncope following the 2 mg dose took two doses within a four-hour period, though neither was his first dose.

TAP evaluated the database to determine if certain patients were more prone to syncope than others. There were no apparent differences between patients having syncopal episodes and those who did not in terms of age, height, weight, race or use of concurrent medications. Nearly all subjects experiencing syncope reported one or more of the following additional adverse events: moderate or severe nausea, sweating, dizziness, vomiting, vasodilatation, and pallor. These data strongly suggest that a prodrome of symptoms occurs prior to the syncopal episodes.

The following table shows the incidence of these adverse events for patients with and without syncope over all Uprima doses (2, 4, 5, 6 mg).

Table 32. Incidence of Prodromal Adverse Events in Patients With and Without Syncope for All Phase I-III Studies (2, 4, 5, 6 mg Uprima)

Symptom		Patients with syncope N= 41 n (%)	Patients without syncope N= 2994 n (%)
Prodrome[+] (All Doses)	Yes	35 (85%)	1043 (35%)
	No	6 (15%)	1951 (65%)
Prodrome[+] (2 and 4 mg Only)	Yes	11 (85%)	298 (15%)
	No	2 (15%)	1686 (85%)
Nausea (Moderate-Severe)	Yes	19 (46%)	403 (13%)
	No	22 (54%)	2591 (87%)
Dizziness	Yes	21 (51%)	609 (20%)
	No	20 (49%)	2385 (80%)
Vomiting	Yes	10 (24%)	281 (9%)
	No	31 (76%)	2713 (91%)
Sweating	Yes	24 (59%)	403 (13%)
	No	17 (41%)	2591 (87%)
Pallor	Yes	11 (27%)	177 (6%)
	No	30 (73%)	2817 (94%)
Vasodilatation	Yes	3 (7%)	178 (6%)
	No	38 (93%)	2816 (94%)

[+] Prodrome is defined as one or more of the following: moderate/severe nausea, dizziness, vomiting, sweating, pallor, or vasodilatation

As illustrated in this table, the majority of patients who experienced syncope (35/41; 85%) had moderate or severe nausea and/or one or more of the prodromal symptoms, including dizziness, vomiting, sweating, pallor, and vasodilatation. In contrast, only 35% of non-syncope patients experienced one of these symptoms at some point during a Uprima study. This difference is even more striking when only the recommended doses of 2 and 4 mg Uprima are considered, as the incidence of prodromal adverse events was 85% in syncope patients versus 15% in patients without syncope.

There were 73,930 administrations of Uprima which did not result in a syncope. Only 2.9% of these administrations resulted in vasovagal prodomal adverse events. In contrast, of the 41 administrations where syncope occurred, 85% were preceded by associated vasovagal adverse events. Thus, less than 3% of Uprima administrations in those studies

resulted in one or more of the prodromal adverse events which may lead the patient to take precautions (e.g., lie down). When only the recommended doses of 2 and 4 mg are considered, the rate for prodromal events drops further to 1.8%.

The Phase II-III studies clearly show a dose-related increase in the frequency of the prodomal vasovagal syndromes. The Phase I data shows somewhat higher mean C_{max} for patients experiencing the prodomal vasovagal syndromes than for patients not experiencing such events. However, some subjects with low C_{max} values have experienced such events, while other patients with high C_{max} values have not.

Syncope rates among four patient subgroups with organic disease were calculated and are displayed in Table 33. In general, syncope rates were similar among patients with organic disease compared to those without.

Table 33. The Incidence of Syncope in Patients with Organic Disease in the Phase II/III Studies (All Doses)

Treatment Group	Number of Patients N	Related Treatment-Emergent Syncope n (%)
History of CAD	368	5 (1.4)
No History of CAD	1953	28 (1.4)
Hypertensive	717	8 (1.1)
Non-Hypertensive	1604	25 (1.6)
Diabetic	367	6 (1.6)
Non-Diabetic	1954	27 (1.4)
BPH	361	8 (2.2)
No BPH	1960	25 (1.3)

While syncopal episodes are a safety concern, there are several mitigating factors which reduce the level of risk associated within these episodes when Uprima is administered for erectile dysfunction than is the case for other approved drugs which cause syncopal events. First, Uprima is taken within 20 minutes prior to planned sexual activity. Typically, a subject will be with a partner after the drug is administered, likely to be in or near a bed with no intention of operating a motor vehicle or heavy machinery. The subject generally will not be alone, so sympathetic support is available. Second, a

prodrome acts as a warning in almost all cases. A variety of symptoms (including moderate to severe nausea, lightheadedness, and diaphoresis among others) usually in combination and of moderate severity provide a warning of the possibility of a syncopal event. If a subject takes appropriate action, such as lying down, his risk of syncope appears to be negligible. These actions do not preclude sexual activity after the symptoms resolve. Third, the period of risk for a syncopal event is very short. All syncopal events connected with Uprima administration have occurred within two hours of dosing, with the majority occurring between 30 and 60 minutes post-dosing. This corresponds to the approximate time of apomorphine peak plasma levels.

While nausea, when severe and suggestive of vomiting can encourage the subject to get up and go to the bathroom, labeling and patient instructions will stress the need to lie down in such situations. These instructions have been utilized in a recently completed clinical trial with 863 patients which evaluated the recommended doses of 2, 3, and 4 mg of Uprima. It is expected that the incidence of syncopal events will be lower in this study than in previous studies.

Many other approved drugs are associated with syncope and have an overall syncope rate greater than 1%. Drugs like Wellbutrin or Xanax, that are prescribed to improve quality of life, report syncope rates of 1.2%[7] and 3.1%[8], respectively. In comparison when Uprima was administered in doses of 2 and 4 mg, the syncope rate was 0.6% when the doses were optimized. It is expected that this rate will drop further with TAP's recommended patient instructions.

9.1.8 Premature Discontinuation Due to Adverse Events

Premature discontinuations due to adverse events are summarized in this section. If multiple adverse events were indicated for an individual patient, that patient is counted once for each of the adverse events but only once in the overall total.

Of the 2379 patients who had at least one dose of Uprima, 271 (11.4%) patients discontinued prematurely from a short or long-term Phase II/III study due at least in part to

an adverse event. The most frequently cited adverse events resulting in premature termination included nausea (5.1%), dizziness (2.5%), sweating (2.4%), and vomiting (1.9%). Most of these events occurred while patients were on 5 or 6 mg Uprima. For instance, in the Phase III crossover studies, a smaller percentage of patients discontinued following 2 mg (0.9%) or 4 mg (4.7%) dosing as compared to 5 mg (8.2%) or 6 mg (9.5%).

9.2 Clinical Laboratory Determinations

Hematology, chemistry, and urinalysis laboratory parameters measured during the Uprima studies were analyzed using three different methods. Analyses of mean changes from baseline or mean differences between Uprima and placebo were performed. This type of analysis is sensitive to consistent changes across all patients. In addition, shift tables were constructed which were cross-tabulations of baseline and final visit values using the categories of low, normal, high, and missing. Shift tables help identify the numbers of patients in each treatment for whom there is a change from baseline to the final visit relative to the normal range. Finally, the percentages of patients in each treatment who have values identified as markedly abnormal based on predefined criteria were summarized. This type of analysis is sensitive to extreme values.

In the analyses of the clinical laboratory data, both for individual studies and when data were combined across the Phase II/III studies, there were no clinically important or consistent trends observed. Although there were some statistically significant results, the mean changes from baseline and mean differences among treatments were small, not dose-related, and not considered clinically important. Similarly, the review of shift tables revealed no noteworthy patterns. A small percentage of patients had values that met criteria for being markedly abnormal, but these were not consistently observed for any particular laboratory parameter and were not considered clinically relevant.

Tables 34 and 35 provide the number and percent of patients with one or more markedly abnormally high or low hematology and chemistry value, respectively.

Table 34. Numbers and Percentages of Patients with One or More Markedly Abnormally High or Abnormally Low Hematology Value While on Uprima - All Phase II/III Studies Combined (All Doses)

Hematology Parameters	n/N	%
Hemoglobin (g/dL)		
Abnormally High (> 18.5)	2/2104	0.1
Abnormally Low (<11.5 or decrease > 2.5)	7/2104	0.3
Hematocrit (%)		
Abnormally High (>55)	3/2104	0.1
Abnormally Low (<37)	36/2104	1.7
Red Blood Cells (x10E6/ul)		
Abnormally High (>7.0)	0/2104	0
Abnormally Low (<3.8)	15/2104	0.7
MCV (fL)		
Abnormally High (>116.4)	1/2059	<0.1
Abnormally Low (<63.2)	1/2059	<0.1
MCH (PG/cell)		
Abnormally High (>40.8)	0/2059	0
Abnormally Low (<20.8)	1/2059	<0.1
MCHC (gHb/dl)		
Abnormally High (>44.4)	0/2059	0
Abnormally Low(<24.8)	0/2059	0
White Blood Cells (x10E3/ul)		
Abnormally High (>16)	3/2104	0.1
Abnormally Low (<2.8)	3/2104	0.1
Platelet Count (x10E3/ul)		
Abnormally High (>700)	1/2088	<0.1
Abnormally Low (<75)	0/2088	0
Neutrophils (%)		
Abnormally Low (<15)	0/2070	0
Lymphocytes (%)		
Abnormally High (>70)	0/2070	0
Monocytes (%)		
Abnormally High (>15)	12/2070	0.6
Eosinophils (%)		
Abnormally High (>10)	55/2070	2.7
Basophils (%)		
Abnormally High (>5)	0/2070	0

The table above shows that there are no results of note for hematology parameters for patients with either abnormally high or low values.

Table 35. Number and Percentages of Patients With One or More Abnormally Markedly High or Low Chemistry Value While on Uprima - All Phase II/III Studies Combined (All Doses)

Chemistry Parameter	n/N	%
Glucose (mg/dL)		
Abnormally High (>250)	54/2121*	2.5
Abnormally Low (<45)	1/2121**	<0.1
Blood Urea Nitrogen (mg/dL)		
Abnormally High (>30)	21/2121	1.0
Creatinine (mg/dL)		
Abnormally High (>2)	5/2121	0.2
Uric Acid (mg/dL)		
Abnormally High (>10.5)	8/2121	0.4
Sodium (mEq/L)		
Abnormally High (>150)	3/2121	0.1
Abnormally Low (<125)	1/2121	<0.1
Potassium (mEq/L)		
Abnormally High (>6)	0/2121	0
Abnormally Low (<2.8)	1/2121	<0.1
Chloride (mEq/L)		
Abnormally High (>120)	1/2121	<0.1
Abnormally Low (<85)	0/2121	0
Calcium (mg/dL)		
Abnormally High (>11.5)	0/2121	0
Abnormally Low (<7.5)	0/2121	0
Inorganic Phosphorus (mg/dL)		
Abnormally High (>5.5)	3/2107	0.1
Abnormally Low (<1.5)	0/2107	0
Total Protein (g/dL)		
Abnormally Low (<5)	0/2121	0
Albumin (g/dL)		
Abnormally Low (<2.5)	0/2121	0
Total Bilirubin (mg/dL)		
Abnormally High (>2)	16/2121	0.8
Alkaline Phosphatase (IU/L)		
Abnormally High (>363)	0/2121	0
SGOT (IU/L)		
Abnormally High (>111)	5/2121	0.2
SGPT (IU/L)		
Abnormally High (>138)	4/2121	0.2
LDH (IU/L)		
Abnormally High (>816)	1/2121	<0.1

* 53 out of 54 were known diabetic patients
** Diabetic patient

Table 35. Number and Percentages of Patients With One or More Abnormally Markedly High or Low Chemistry Value While on Uprima - All Phase II/III Studies Combined (All Doses) (Cont.)

Chemistry Parameter	n/N	%
GGT (IU/L)		
Abnormally High (>192)	11/2078	0.5
Cholesterol (mg/dL)		
Abnormally High (>350)	2/2101	0.1
Triglycerides (mg/dL)		
Abnormally High (>798)	16/2077	0.8

Note: Only patients who have both a pre-dose and post-dose value are included.

For all the chemistry parameters, the percentage of patients with abnormally high or low values was not clinically significant. Similar results were also seen for urinalysis parameters.

In conclusion, although occasional changes in laboratory variables were observed for hematology, chemistry, and urinalysis variables, these changes were not considered clinically meaningful and were not related to dosing with Uprima.

9.3 Vital Signs

For all studies, vital sign measurements, including systolic and diastolic blood pressure and pulse rate, were taken prior to dosing and at various post-dosing visits. For the Phase II/III studies, vital signs were typically measured while sitting and were done at scheduled study visits but not necessarily immediately after dosing. For the Phase I studies, including the Phase I alcohol interaction studies and the antihypertensive and nitrates study, vital signs were taken at multiple time points both prior to and following a dose. Both supine and standing measurements were taken.

9.3.1 Vital Signs in Phase II/III Studies

In the Phase II/III studies, there were small mean fluctuations in vital signs parameters which primarily reflected small reductions in blood pressure. A few statistically significant differences were observed but no consistent trends or clinically meaningful changes were noted for any parameter.

For one of the Phase III crossover studies, M98-941, measurements of standing and supine pulse and of standing and supine systolic and diastolic blood pressure were obtained prior to dosing and at 10, 20, 30, 40, 50 minutes and 1, 1.25, 1.5, 1.75, and 2 hours after the first (in-office) dose in each study period. Changes from baseline in both supine and standing measurements were determined for each timepoint as well as the maximum drop from baseline across timepoints. For standing and supine pulse, there were no statistically significant differences between Uprima and placebo for the 2, 4, or 5 mg arms at any timepoint. In the 2 mg and 4 mg arms for standing and supine systolic and diastolic blood pressures, there were sporadic statistically significant differences observed at a few timepoints when comparing Uprima to placebo; however, no consistent or clinically relevant trends were noted. In the 5 mg arm for standing and supine systolic and diastolic blood pressures, there were statistically significant differences between Uprima and placebo for a number of timepoints. However, the mean decreases for Uprima 5 mg were small (less than 2 mm Hg for diastolic blood pressure and less than 8 mm Hg for systolic blood pressure), and therefore these changes were not considered clinically significant. The results of the maximum drop from baseline were similar.

9.3.2 Vital Signs in Phase I Alcohol Interaction Studies

Four interaction studies with Uprima and ethanol were conducted: M97-745 (Uprima 5 mg and 0.6 g/kg ethanol), M97-762 (Uprima 6 mg and 0.15 g/kg ethanol), M98-838 (Uprima 6 mg and 0.3 g/kg ethanol), and M98-891 (Uprima 6 mg and 0.6 g/kg ethanol). The top dose of ethanol (0.6 g/kg) is equivalent to four to six 1 ounce shots, depending on

body weight in this study (roughly equivalent to 2 six-ounce glasses of wine or three 12 ounce beers). It was consumed over a 30 minute time period, 30 minutes prior to administration of Uprima or placebo.

For all of the Phase I alcohol interaction studies, there was little indication of any effect on vital signs when Uprima was administered without alcohol, as both mean changes from baseline and changes from supine to standing were small and not clinically significant. However, the combination of Uprima at a higher than recommended dose (6 mg) with ethanol suggests the possibility of a pharmacodynamic interaction with greater decreases in standing systolic and diastolic blood pressure.

In Study M98-891, which combined 6 mg Uprima with 0.6 g/kg of ethanol, significant differences among regimens were noted for mean changes from baseline to 45 minutes post-dosing for both standing systolic and diastolic blood pressures, with greater decreases from baseline observed in the Uprima/ethanol regimen (-15.90 and -9.93 mmHg) as compared to ethanol alone (-1.17 and 1.44 mmHg) and Uprima alone (-4.15 and –0.04 mmHg). These statistically significant results correspond to the approximate time of peak plasma concentrations of apomorphine and therefore suggest a clinically meaningful interaction. Furthermore, the incidences of abnormally low standing systolic (<80 mmHg) and diastolic (<40 mmHg) blood pressures were higher in the combination regimen (20.3% and 14.1%) than for either Uprima (1.5% for both) or ethanol (1.6 % for both) alone. The results of M97-745 (Uprima 5 mg and 0.6 g/kg ethanol) were similar with respect to both mean reductions in blood pressure and incidence of abnormally low blood pressure values.

For 6 mg Uprima and 0.3 g/kg ethanol (Study M98-838), similar trends were seen but to a much lesser extent. Although mean decreases in standing blood pressure were higher for the Uprima/ethanol regimen than for either regimen alone, differences among regimens were not statistically significant at any post-dosing timepoint (significance was only achieved when analyzing the greatest drop across all timepoints). In addition, the

incidences of abnormally low systolic and diastolic blood pressure values were somewhat higher in the combination regimen (11.9% and 7.5%) than for either regimen alone (0.0% to 4.5%), but much less so than in M98-891 (6 mg Uprima, 0.6 g/kg ethanol).

For M97-762, the study that evaluated 0.15g/kg ethanol, there were no clinically meaningful differences between regimens.

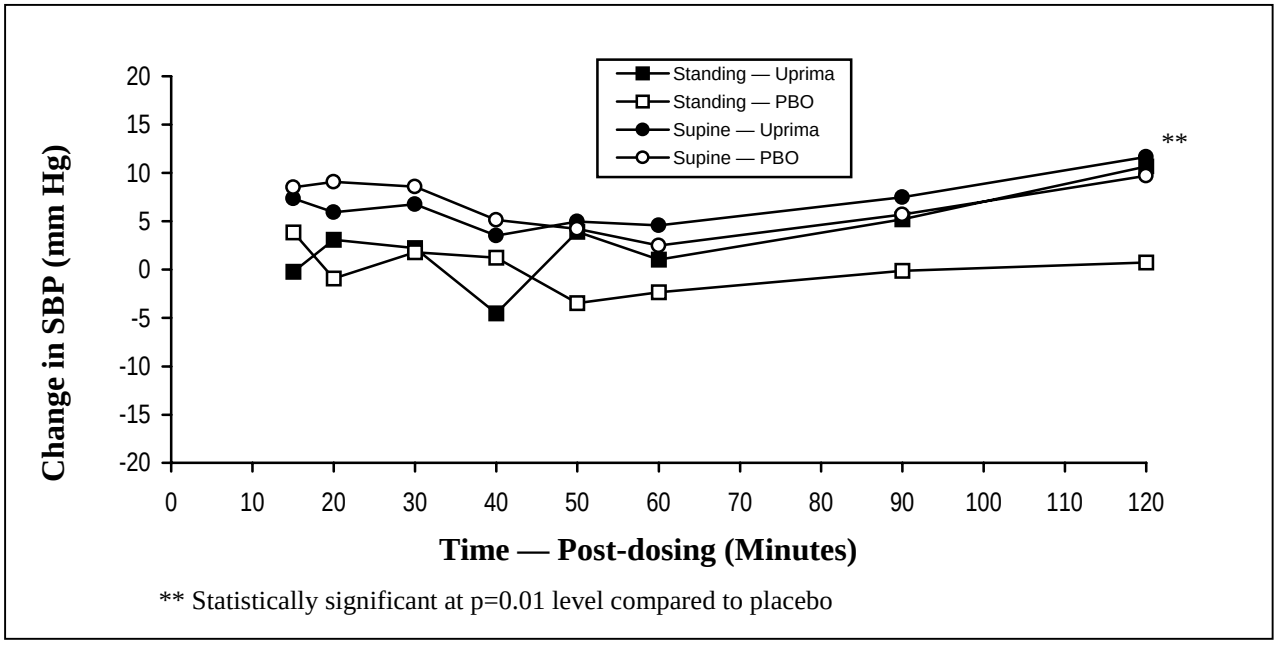
Results of the alcohol studies suggest a potential for a clinically important pharmacodynamic interaction between a higher than recommended dose of Uprima (6 mg) and the highest studied dose of ethanol (0.6g/kg). At the lowest dose of ethanol studied (0.15g/kg), no evidence of interaction was observed. For the middle dose (0.3g/kg), some trends were seen but the actual mean differences observed were neither statistically significant at the time of peak plasma levels nor clinically important. Product labeling will recommend that Uprima may be taken following moderate alcohol ingestion.

9.3.3 Vital Signs in the Phase I Antihypertensive/Nitrate Study

At the request of the FDA, a study to evaluate the pharmacodynamic interaction between Uprima and antihypertensives/nitrates was conducted. This study, M98-930, was a two-period crossover study comparing Uprima 5 mg and placebo in subjects with underlying cardiovascular disease who were receiving antihypertensive (ACE inhibitors, beta-blockers, diuretics, calcium channel blockers, $alpha_1$ blockers) or nitrate (short- and long- acting) medications. Vital signs and Holter monitor recordings were performed both before and after dosing to assess potential cardiovascular effects.

The analyses of mean changes from supine to standing as well as mean changes from baseline in vital sign measurements yielded sporadic statistically significant differences between Uprima 5 mg and placebo across the five antihypertensive dosing groups. These differences, however, were not considered clinically significant or indicative of a clinically meaningful trend. These results are illustrated in Figures 22 through 31.

Figure 22. Ace Inhibitors — Mean Change from Baseline in Systolic Blood Pressure



** Statistically significant at p=0.01 level compared to placebo

Figure 23. Ace Inhibitors — Mean Change from Baseline in Diastolic Blood Pressure

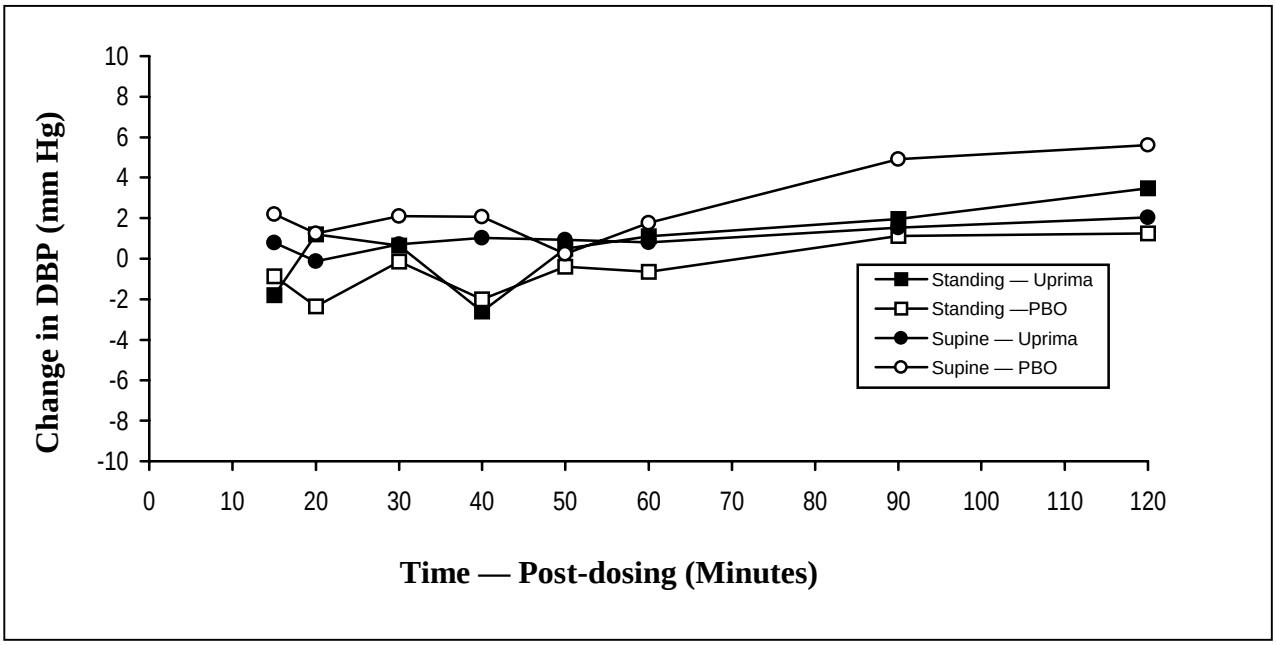
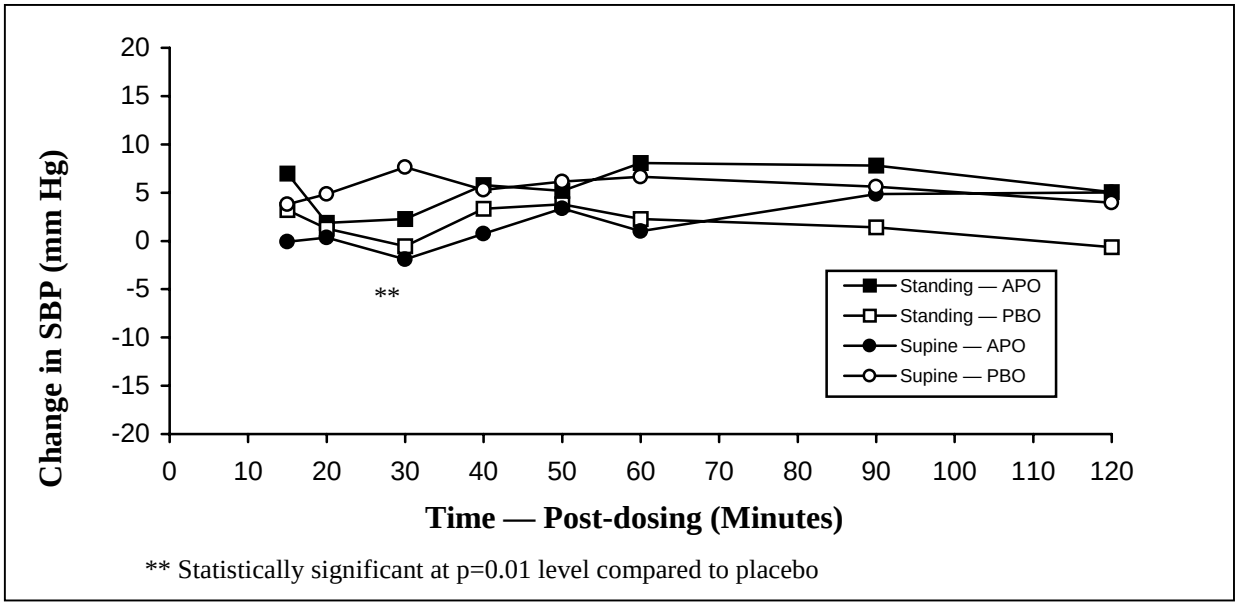
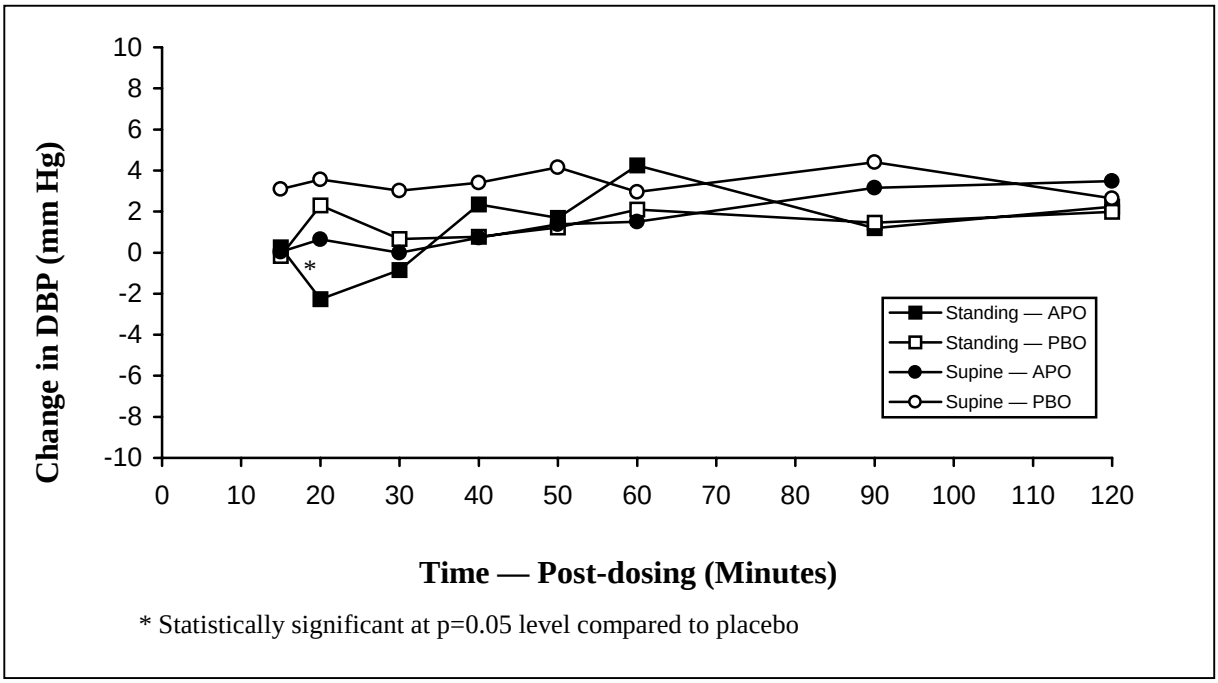


Figure 24. Beta Blockers — Mean Change from Baseline in Systolic Blood Pressure



** Statistically significant at p=0.01 level compared to placebo

Figure 25. Beta Blockers — Mean Change from Baseline in Diastolic Blood Pressure



* Statistically significant at p=0.05 level compared to placebo

Figure 26. Diuretics – Mean Change from Baseline in Systolic Blood Pressure

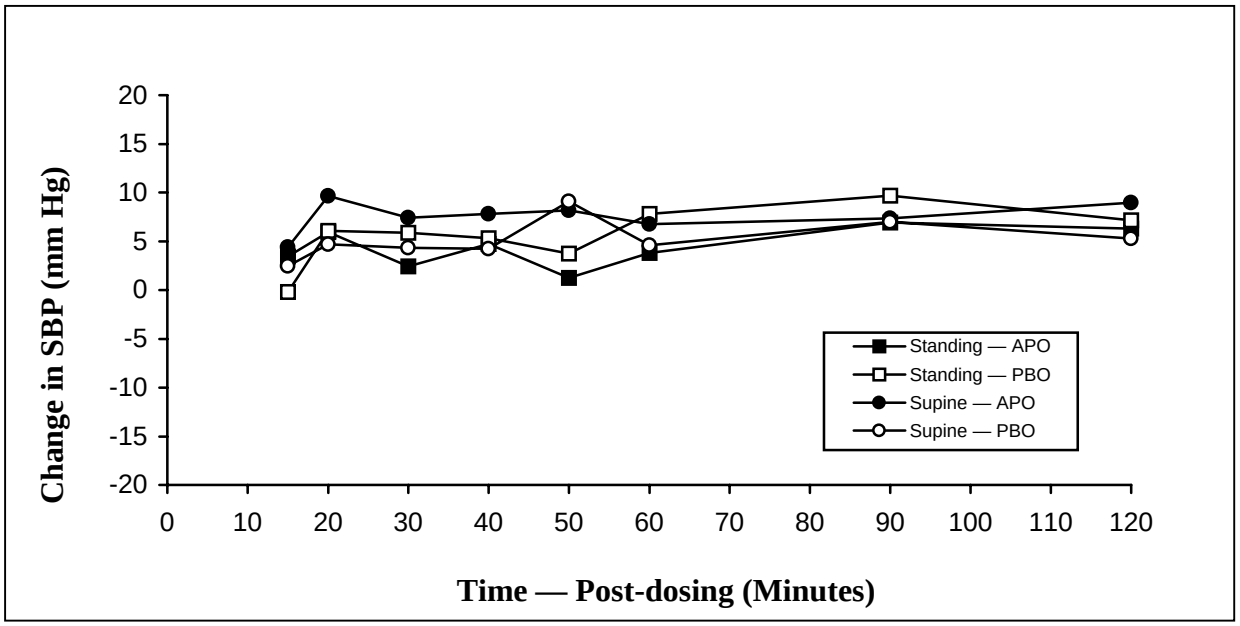


Figure 27. Diuretics — Mean Change from Baseline in Diastolic Blood Pressure

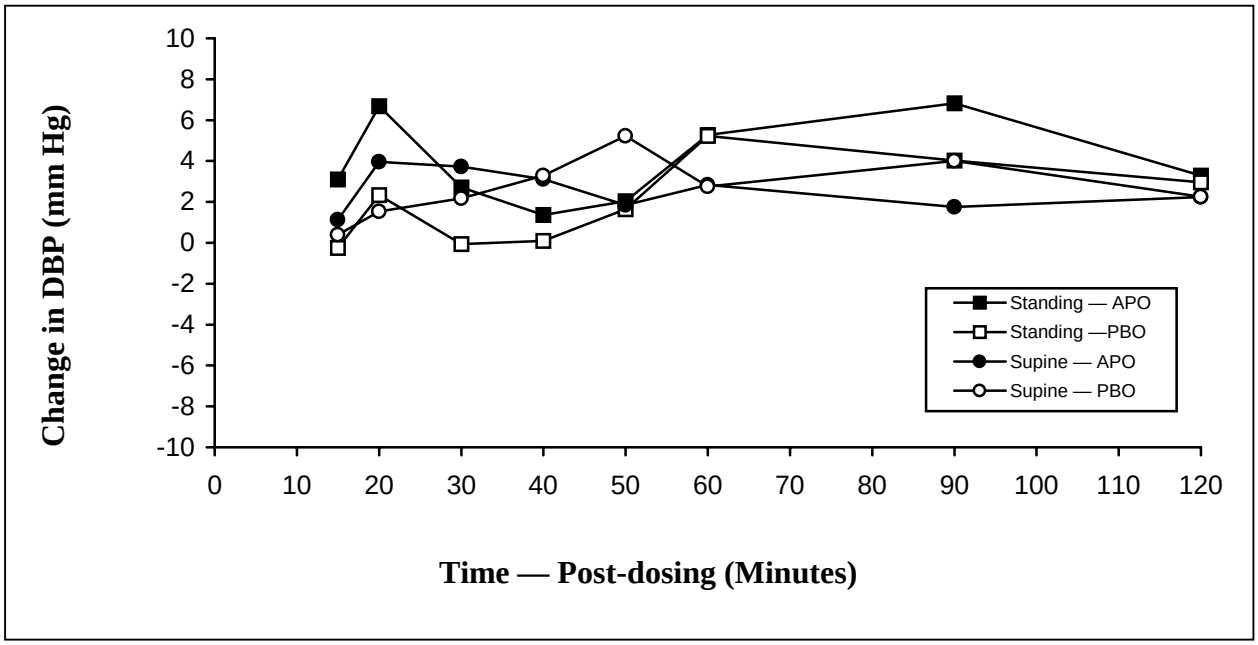
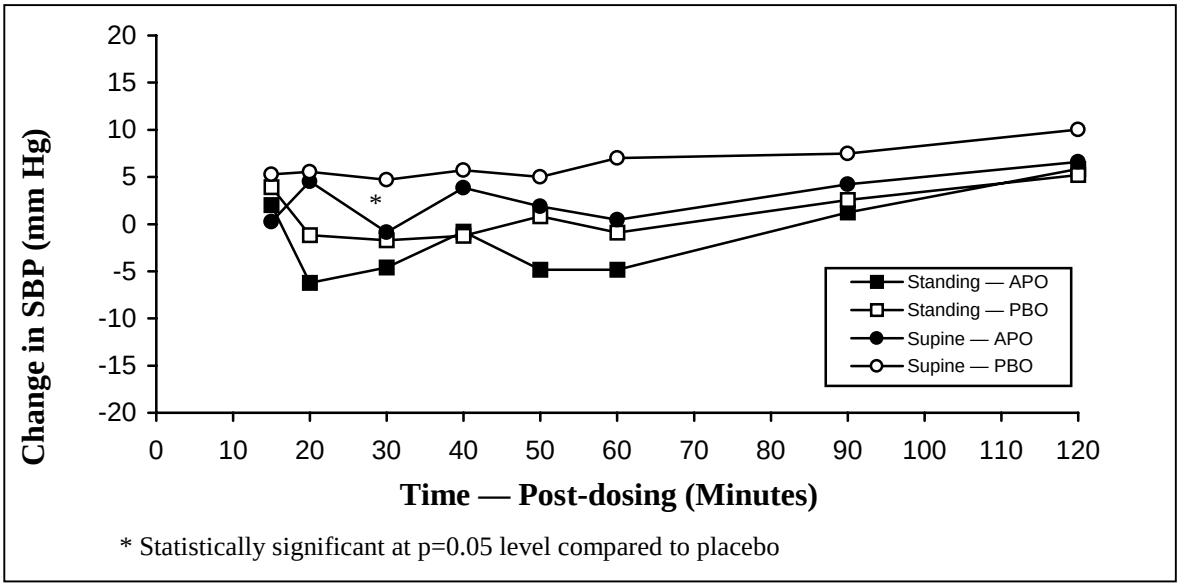


Figure 28. Calcium Channel Blockers — Mean Change from Baseline in Systolic Blood Pressure



* Statistically significant at p=0.05 level compared to placebo

Figure 29. Calcium Channel Blockers — Mean Change from Baseline in Diastolic Blood Pressure

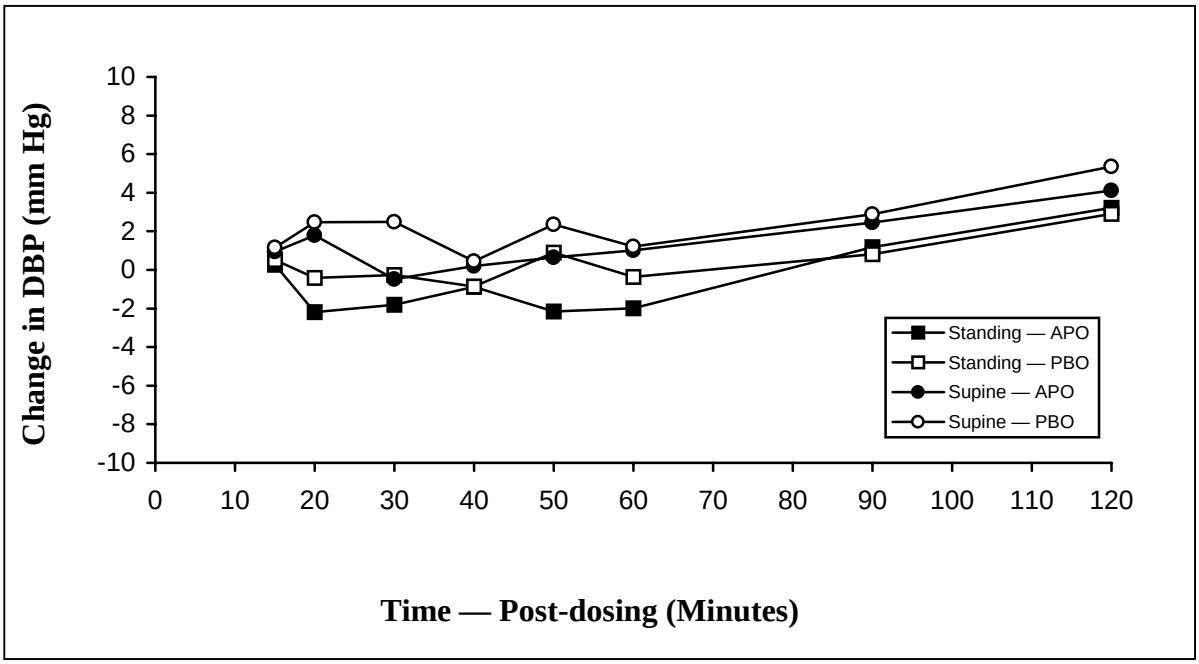


Figure 30. Alpha$_1$ Blockers — Mean Change from Baseline in Systolic Blood Pressure

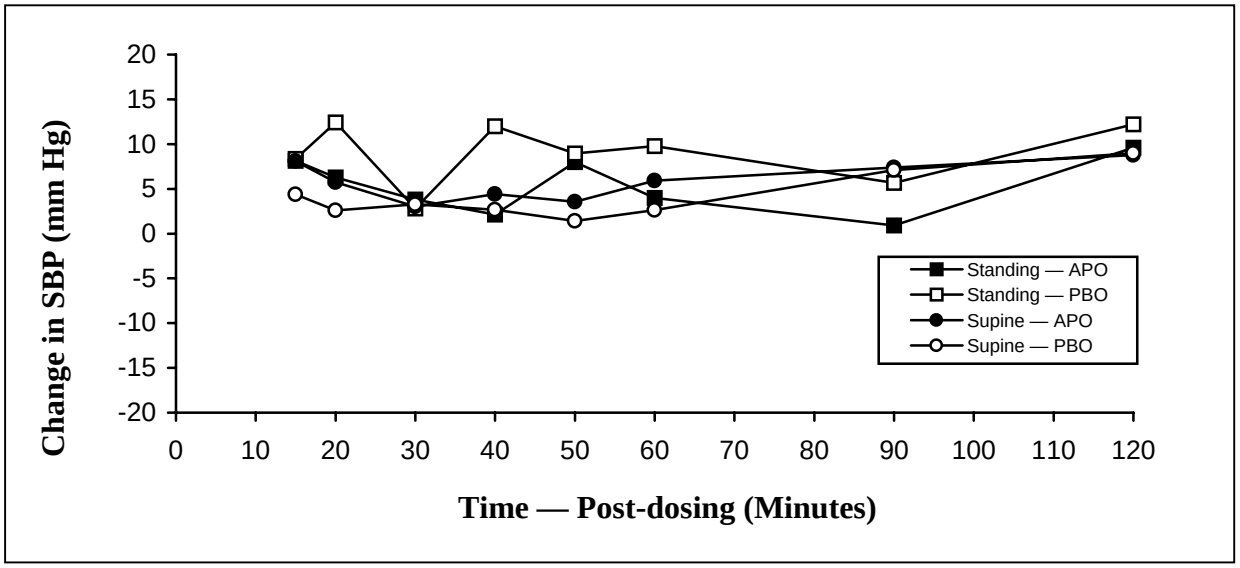
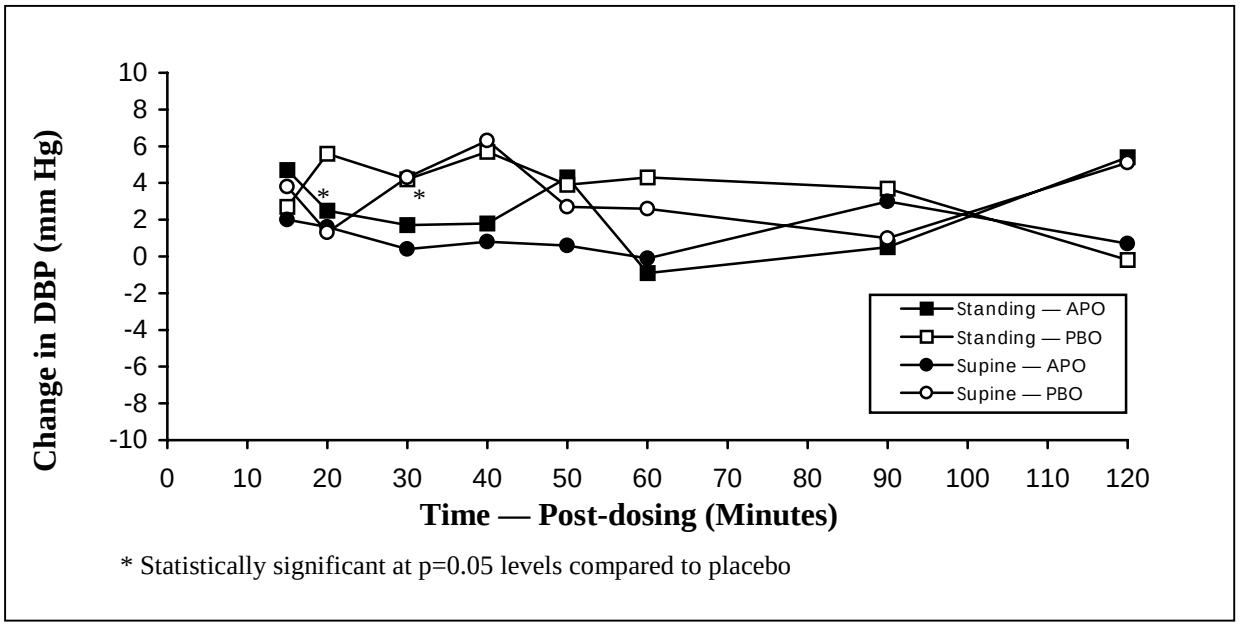


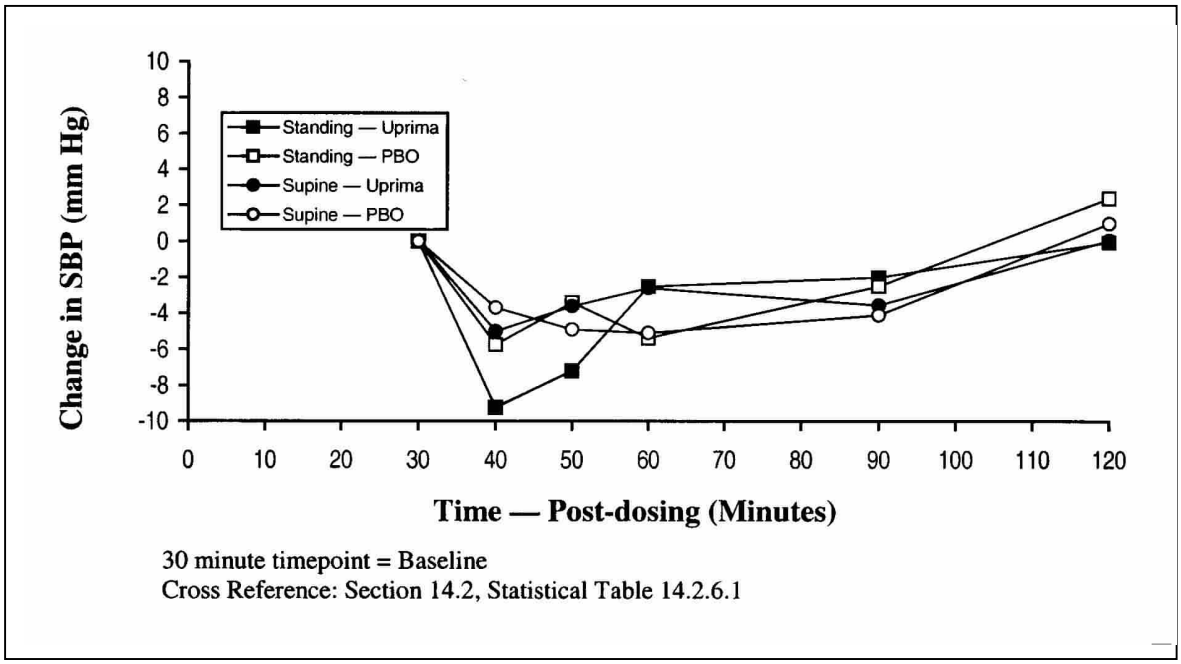
Figure 31. Alpha$_1$ Blockers — Mean Change from Baseline in Diastolic Blood Pressure



* Statistically significant at p=0.05 levels compared to placebo

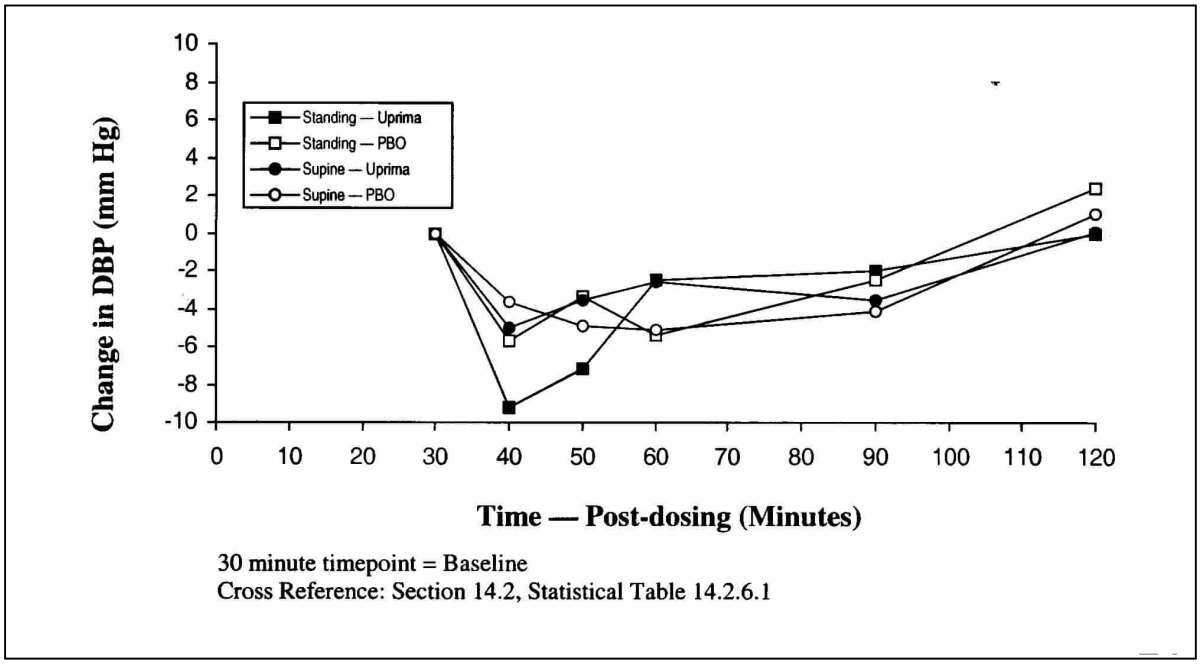
For the long-acting nitrate group, there were several significant differences between Uprima 5 mg and placebo in standing systolic blood pressures, some of which occurred during the approximate time of peak apomorphine 5 mg plasma concentrations. In all of these cases, however, the mean decreases from baseline for the Uprima group were relatively small (less than 10 mm Hg). Moreover, for the mean change from baseline analyses, the significance seen for blood pressure was driven as much by the increases from baseline for placebo as the decreases seen for Uprima. No clinically meaningful mean differences were observed in the short-acting nitrate group. The results for the two nitrate groups are shown in Figures 32 through 35.

Figure 32. Short-Acting Nitrates – Mean Change from Baseline in Systolic Blood Pressure



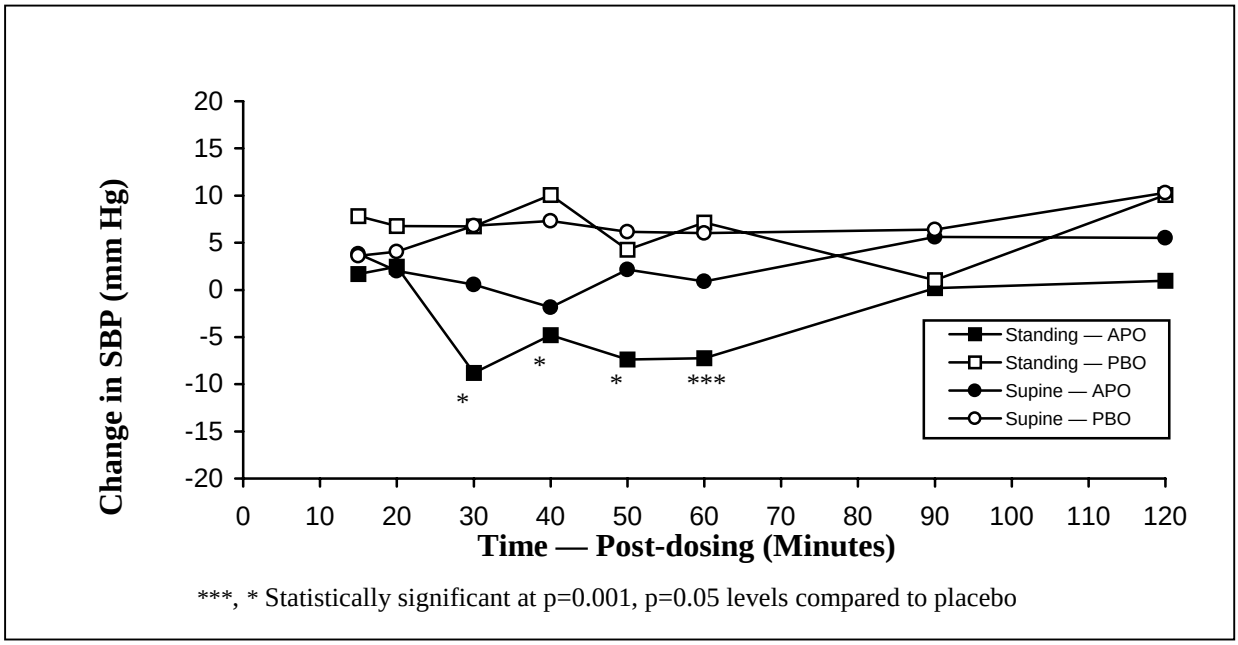
30 minute timepoint = Baseline
Cross Reference: Section 14.2, Statistical Table 14.2.6.1

Figure 33. Short-Acting Nitrates — Mean Change from Baseline in Diastolic Blood Pressure



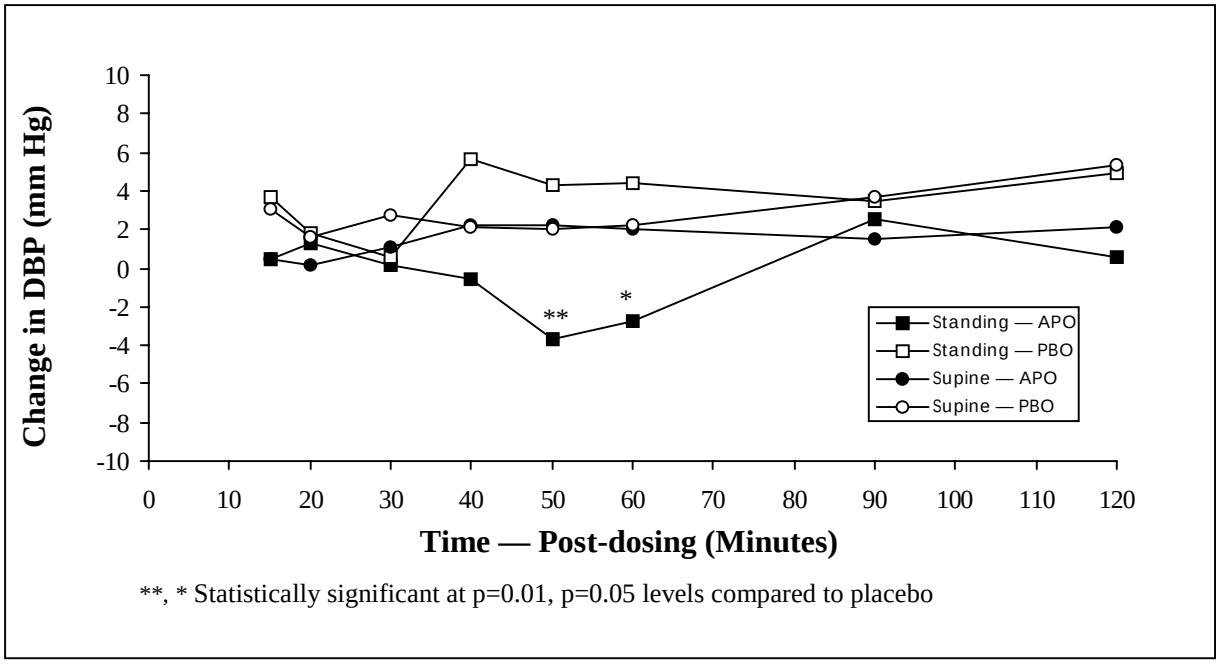
30 minute timepoint = Baseline
Cross Reference: Section 14.2, Statistical Table 14.2.6.1

Figure 34. Long-Acting Nitrates — Mean Change from Baseline in Systolic Blood Pressure



***, * Statistically significant at p=0.001, p=0.05 levels compared to placebo

Figure 35. Long-Acting Nitrates — Mean Change from Baseline in Diastolic Blood Pressure



**, * Statistically significant at p=0.01, p=0.05 levels compared to placebo

In both the short- and long-acting nitrate groups, clinically significant symptomatic decreases in standing blood pressure were observed in a small number of subjects (4 of 40) in association with vasovagal adverse events. Despite this, none of these subjects, each of whom had significant underlying cardiovascular disease and were taking multiple cardiovascular medications, experienced a clinically significant Holter monitor abnormality, and no patient experienced a syncopal episode. Moreover, these blood pressure changes and associated vasovagal type adverse events were similar to those reported in patients who experienced vasovagal type adverse events in other Uprima studies.

Overall, Uprima 5 mg was found to be safe and well-tolerated and did not significantly alter the blood pressure or pulse in the majority of subjects who were concurrently being treated with ACE inhibitors, beta-blockers, diuretics, calcium channel blockers, alpha$_1$ blockers or short and long-acting nitrates.

9.4 Pharmacokinetic - Cardiovascular Pharmacodynamic Correlations

The relationship of blood pressure and pulse rate changes with apomorphine C_{max} and AUC in selected Phase I studies are described in this section. Pharmacokinetic and vital sign data from the following seven Phase I studies with Uprima (2, 4, 5 or 6 mg; F2 formulation) were used to investigate the relationship of change from baseline in blood pressure and pulse rate with apomorphine C_{max} and AUC.

Table 36. Phase I Studies

Study	Design	Regimens Used in Correlation Investigation	n
M97-745: Interaction effect of ethanol (0.6 g/kg) on apomorphine	Crossover	5 mg Uprima + placebo beverage	7
M97-794: Formulation/manufacturing site comparison	Crossover	6 mg Uprima F2 formulation, Oread and AAI	24
M98-815: Effect of Zofran® and Compazine® on apomorphine	Crossover	6 mg Uprima alone	71
M98-843: Elderly vs Young	Parallel	5 mg Uprima	2 x 48
M98-844: PK and bioavailability of 2, 4, 5 and 6 mg Uprima (F2 formulation) vs 1 mg SC	Crossover	2, 4, 5, and 6 mg Uprima	24
M98-838: Uprima - Ethanol (0.3 g/kg) interaction	Crossover	6 mg Uprima + placebo beverage	65
M98-891: Uprima - Ethanol (0.6 g/kg) interaction	Crossover	6 mg Uprima + placebo beverage	62

Observations made within four hours of dosing were used for the supine or sitting cardiovascular measurements and AUC determinations to preclude an effect from lunch, which was served at 4 or 5 hours post-dosing. The last measurement of blood pressure or pulse rate taken prior to dosing in each period was used as the baseline value. Parameters used in this analysis included the mean and minimum of change from baseline in systolic and diastolic blood pressure and pulse rate measurements, the maximum of change from baseline in pulse rate, apomorphine C_{max} and $AUC_{4\,h}$.

There was no statistically significant correlation between change from baseline in systolic or diastolic blood pressure and $AUC_{4\,h}$ or C_{max}. The mean and maximum change from baseline in pulse rate were statistically significantly correlated with C_{max} and $AUC_{4\,h}$. However, the results of this analysis indicated that only a small change in pulse rate would be expected from a rather large increase in apomorphine C_{max} or $AUC_{4\,h}$. A 10 ng·h/mL increase in AUC_{4h} or a 6 ng/mL increase in C_{max} would be expected to result in a 4 beat per minute (bpm) increase in the expected value of the mean change in pulse rate or a 10 bpm increase in the expected value of the maximum change in pulse rate. C_{max} and $AUC_{4\,h}$ increases of that magnitude would represent substantial increases over the maximal C_{max} and $AUC_{4\,h}$ values (5.9 ng/mL and 8.3 ng·h/mL) observed in these studies and would be associated with increases in pulse rate that would probably have little, if any, clinical significance.

There was also a statistically significant age effect for the mean and maximum of change from baseline in pulse rate. With a 10 year increase in age, the maximum increase in pulse rate with Uprima would be reduced by an estimated 1.4 bpm, on average, while attenuation in the mean increase would be less remarkable.

Overall, the results of this analysis suggest that there is no association between blood pressure measurements and apomorphine concentration variables, while a slight positive correlation exists between pulse rate and C_{max} and AUC. Age has a statistically significant negative effect on the mean and maximum increase in pulse rate, *i.e.*, the apomorphine-induced small increase in pulse diminishes as age increases.

9.5 Physical Examinations and ECG Results

Physical examinations and ECG's were conducted during the Phase II/III Studies at baseline (prior to dosing) and at the Final Visit. Periodic examinations were also conducted in the Phase III studies during the course of treatment. In the Phase I alcohol interaction studies, physical examinations and ECG's were conducted at baseline and prior to discharge from the study. All clinically significant physical examination and ECG changes which worsened from baseline status were documented as adverse events and recorded on an adverse event case report form.

Few patients exhibited clinically significant physical examination changes during the Uprima studies. Among the 113 patients (5%) who did, most of the changes were not related to study drug and all were documented as adverse events. Six of 2379 patients experienced ECG changes which were clinically significant and considered by the investigator to be possibly related to study drug. However, none of these patients experienced a change which was plausibly related to Uprima treatment; four of the patients had the abnormal ECG several days after taking their last Uprima dose (one of whom also had evidence of underlying myocardial disease at the baseline ECG), and two patients had clinically significant ECG changes after receiving placebo.

9.6 Holter Monitor Safety Assessment

TAP revised several protocols to more adequately assess the cardiovascular status of subjects/patients to determine whether Uprima produced any direct cardiac effects, particularly during a syncopal episode. These revisions included the addition of Holter monitoring (for one hour prior to dosing and two hours post-dosing) in the Phase I alcohol interaction studies M98-838 and M98-891 and the Phase I pharmacokinetic study M98-844. In addition, the protocol for the Phase III diabetic study M97-804 was also amended to include Holter monitoring at four centers. At the recommendation of

FDA, a Phase I pharmacodynamic study was initiated to examine the interaction between Uprima and various antihypertensives and nitrates (M98-930) and included Holter monitoring.

A total of 1702 Holter recordings were obtained from 344 subjects/patients participating in five Uprima studies (M97-804, M98-838, M98-891, M98-930 and M98-844). Holter abnormalities were noted in 17 subjects (4.9%) after Uprima dosing; in addition, 11 patients had Holter abnormalities prior to dosing or while on placebo (3.2%). Five subjects experienced abnormal readings following both Uprima and placebo administration. The most common abnormalities were sinus pauses and junctional rhythm, both of which were reported with similar frequency among Uprima–treated subjects as compared to placebo or prior to dosing. Sinus pauses occurring after Uprima administration ranged from 2.0 to 10.1 seconds. Such pauses up to 11.0 seconds have been associated with increased vagal tone due to vomiting.[9] The longest sinus pause observed during the study (19.8 seconds) occurred during a blood draw prior to dosing and was therefore not associated with Uprima.

The abnormal findings in subjects treated with Uprima were usually associated with signs and symptoms such as nausea, diaphoresis and lightheadedness at a time when Uprima peak plasma levels occur (25-50 minutes post dose). The same signs and symptoms were recorded on other study days when Uprima was administered and no abnormal Holter findings were recorded.

In conclusion, Uprima, either alone or in combination with alcohol or antihypertensives, does not appear to have any effect on cardiac rhythm, other than those mediated through a vasovagal effect in a small percentage of patients. None of these was considered to be serious or life-threatening by the investigator.

9.7 Profile of Mood States (POMS)

The POMS questionnaire was completed by patients in Study M96-470 to assess any changes in mood states. The questionnaire was completed by each patient prior to the first dose of study drug and at the end of each crossover period.

The results of the POMS revealed no significant differences between Uprima and placebo for any index for any dose. The mean POMS indices for placebo and Uprima for each dose can be found in Table 37.

Table 37. Profile of Mood States Questionnaire Results in the Phase III Crossover Study (M96-470)

	2 mg Group		4 mg Group		6 mg Group	
Index (36-0)	**Placebo Mean**	**Uprima Mean**	**Placebo Mean**	**Uprima Mean**	**Placebo Mean**	**Uprima Mean**
Composed – Anxious	27.0	27.3	28.0	27.6	27.2	26.7
Agreeable – Hostile	29.9	30.0	29.5	29.5	28.9	28.6
Elated – Depressed	27.6	27.6	27.1	27.4	27.4	27.1
Confident – Unsure	27.4	27.8	27.6	28.0	26.4	26.2
Clearheaded – Confused	30.3	30.7	30.8	31.0	30.0	30.0
Energetic – Tired	27.0	27.0	26.0	26.2	25.6	25.3

All mood states range from 36 (best) to 0 (worst).

9.8 Concurrent Medications

The use of concurrent medications was defined according to each study protocol. Medications taken by patients during the course of study participation were either reported by patients or recorded by the investigator via interview during a clinic visit.

The Phase II/III studies were designed to incorporate optional use of antiemetics to treat nausea and vomiting, which are expected side effects of Uprima administration. The majority of patients in the studies required no antiemetic medication, and most patients who did required only one or two doses. Patients treated with 2 or 4 mg Uprima or with dose-optimization required fewer antiemetics than patients treated with 5 or 6 mg fixed doses.

Table 38 shows antiemetic medications use for the Phase III crossover studies.

Table 38. Antiemetic Medication Use by Treatment Group in the Phase III Crossover Studies (M96-470, M97-658 and M98-941)

Treatment	Number of Patients	Antiemetic Usage			
		None n (%)	1-2 Doses n (%)	3-6 Doses n (%)	>6 Doses n (%)
Uprima 2 mg	429	427 (99.5)	2 (0.5)	0 (0.0)	0 (0.0)
Placebo	436	435 (99.8)	1 (0.2)	0 (0.0)	0 (0.0)
Uprima 4 mg	426	403 (94.6)	8 (1.9)	6 (1.4)	9 (2.1)
Placebo	414	409 (98.8)	2 (0.5)	1 (0.2)	2 (0.5)
Uprima 5 g	282	253 (89.7)	15 (5.3)	6 (2.1)	8 (2.8)
Placebo	263	263 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uprima 6 mg	262	214 (81.7)	19 (7.3)	14 (5.3)	15 (5.7)
Placebo	236	235 (99.6)	1 (0.4)	0 (0.0)	0 (0.0)

Table 39 presents the most frequent concurrent medications taken by patients in the Phase II/III studies. Analgesics, antipyretics and anti-inflammatory agents were the most frequently used concomitant medications in the Phase II/III studies. Coagulants and anticoagulants and hypotensive agents were also used frequently.

Table 39. Concurrent Medication Use Reported by ≥ 5% of Uprima Patients by MedClass in the Phase II/III Studies

Concurrent Medication Level 1 Class Level 2 Class	Uprima Patients N=2379 n (%)
Any Medication	2,155 (90.6)
Anti Infective Agents	
Antibiotics	520 (21.9)
Urinary anti-infectives	120 (5.0)
Antihistamine Drugs	
Antihistamine drugs	389 (16.4)
H_1 –Receptor antagonists	534 (22.4)
Antitussives, Expectorants, and Mucolytic Agents	
Antitussives	376 (15.8)
Expectorants	184 (7.7)
Autonomic Drugs	
Anticholinergic agents	336 (14.1)
Sympathomimetic agents	490 (20.6)
Sympatholytic agents	125 (5.3)
Blood Formation and Coagulation	
Antianemia drugs	126 (5.3)
Coagulants and anti-coagulants	814 (34.2)
Cardiovascular Drugs	
Hypotensive agents	715 (30.1)
Cardiac drugs	503 (21.1)
Antihyperlipidemic agents	416 (17.5)
Central Nervous System Agents	
Analgesics, antipyretic, and anti-inflammatory agents	1,455 (61.2)
Anticonvulsants	176 (7.4)
Psychotherapeutic agents	438 (18.4)
Anxiolytics, sedatives and hypnotics	356 (15.0)
Electrolytic, Caloric, and Water Balance	
Acidifying agents	281 (11.8)
Caloric agents	650 (27.3)
Diuretics	227 (9.5)
Replacement preparations	220 (9.2)
Eye, Ear, Nose and Throat Preparations	
Nasal decongestants	463 (19.5)
Anti-inflammatory agents	146 (6.1)
Gastrointestinal Drugs	
Antacids and absorbents	171 (7.2)
Antiemetics	409 (17.2)
Cathartics and laxatives	226 (9.5)
Gastrointestinal drugs	154 (6.5)
Histamine H_2-receptor antagonists	174 (7.3)

Table 39. Concurrent Medication Use Reported by ≥ 5% of Uprima Patients by MedClass in the Phase II/III Studies (Cont.)

Concurrent Medication Level 1 Class Level 2 Class	Uprima Patients N=2379 n (%)	
Hormones and Synthetic Substitutes		
Adrenal corticosteroids	217	(9.1)
Antidiabetic agents	330	(13.9)
Thyroid and Antithyroid agents	133	(5.6)
Skin and Mucous Membrane Agents		
Anti-infectives	217	(9.1)
Antipruritics	308	(13.0)
Anti-inflammatory agents	199	(8.4)
Antiseborrheic agents	161	(6.8)
Smooth Muscle Relaxants		
Respiratory smooth muscle relaxants	123	(5.2)
Vitamins and Other Nutrients		
Minerals and electrolytes, oral	254	(10.7)
Vitamins and other nutrients	560	(23.5)
Multi-vitamin preparations	409	(17.2)
Vitamin and mineral combinations	405	(17.0)
Vitamin B complex	149	(6.3)
Vitamin C	264	(11.1)
Vitamin E	319	(13.4)

For each of the most frequently reported (>10%) concurrent medication classes in the Phase III crossover studies, analyses were done for each dosing arm that tested whether the differences in adverse event rates between Uprima and placebo were similar for patients who took concurrent medications compared to those who did not. The most frequently reported medication classes were: analgesics, antipyretics and anti-inflammatory agents; psychotherapeutic agents (which includes compazine); and antiemetics. Similar analyses were also performed for other important medication classes, including hypotensive agents, cardiac drugs, and autonomic drugs.

The medication classification subgroup analysis revealed only two statistically significant results. For analgesics, antipyretics, and anti-inflammatory agents, the differences between 4 and 5 mg and placebo for nausea were significantly different for patients who reported taking these medications than for those who did not (p-values ≤ 0.031). While patients experienced more nausea on Uprima than placebo, these differences were

slightly smaller among patients who reported taking analgesics, antipyretics or anti-inflammatory agents, primarily due to increased nausea in the placebo patients. No other statistically significant differences or clinically important trends were observed with respect to concurrent medications, in particular for hypotensive agents, cardiac drugs, autonomic drugs and psychotherapeutic agents.

9.9 Safety Conclusions

Overall, the safety analyses of the 27 Phase I-III studies indicate that Uprima is best tolerated at dosages of 2 to 4 mg when the dose is optimized for individual patients. More commonly reported adverse events such as nausea and vomiting, were generally tolerable; most occurrences were mild or moderate in severity, and the majority of patients across all studies required no antiemetic medication during treatment with Uprima. Furthermore, data from the Phase III parallel study suggest that accommodation to adverse events develops, as evidenced by the substantial decrease in adverse events noted during the maintenance period as compared to the dose-optimization period of that study. The most medically significant adverse event was syncope. Nearly all of the syncopal events were associated with a prodrome of vasovagal symptoms which consisted of one or more of the following: moderate to severe nausea, dizziness, vomiting, sweating, pallor and vasodilatation. Appropriate patient instructions related to this prodrome offer an opportunity to minimize the risk of syncope.

Overall, the data suggest that Uprima administered at 2 mg and increasing to a maximum of 4 mg is a safe treatment for erectile dysfunction.

9.10 References

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10.0 Overall Conclusions

Erectile dysfunction (ED) is estimated to affect 30 million men in the United States.[1,2] As well as affecting sexual functioning, many men with ED also report decrements in self-esteem and interpersonal sensitivity, decreases in physical functioning and role functioning as well as increased depression and mental distress.[3,4] Erectile dysfunction has been described as an important public health problem by the National Institutes of Health Consensus Panel.[5,6] With the strong association between sexual dysfunction and impaired quality of life, this problem warrants recognition as a significant public health concern.[6]

Several new drugs offer significant therapeutic potential for the treatment of male erectile dysfunction.[7,8] However, it must be recognized that the etiology of ED is multifactorial and complex requiring different therapeutic approaches. Hence, medical conditions such as ED which are caused by complex mechanisms may require different approaches (different mechanisms of action) to effectively treat patients.

The data presented in this document are the results of the clinical program designed in consultation with the FDA to determine the safety and efficacy of Uprima in the treatment of men with ED. Uprima has been extensively studied in 27 clinical trials with a total 3,035 patients/subjects who received Uprima. This includes eleven Phase II/III studies with a total of 2,379 patients and 16 Phase I studies with a total of 656 subjects. The Phase I studies consist of alcohol interaction studies, drug interaction studies, special population studies and pharmacokinetic and metabolism studies. These studies have provided extensive safety data from patients taking antihypertensive medications as well as patients with diabetes, benign prostatic hyperplasia (BPH), and coronary artery disease.

The Uprima efficacy evaluations encompass both patient and partner assessments including both validated efficacy questionnaires which are completed by the patients and/or partners at the end of treatment and the more “objective” type of efficacy

assessments which are completed after each dose of study drug. These assessments tools made it possible to evaluate the consistency and reproducibility of the efficacy response in both the patient and partner.

In the Phase II/III clinical studies, Uprima was studied in men with ED to evaluate its efficacy in achieving erections firm enough for intercourse according to both the patient and partner. Uprima was evaluated in randomized, double-blind, placebo-controlled studies using a variety of study designs (crossover or parallel, fixed or escalating dose). Uprima has been administered to 2,379 patients with ED of various etiologies including patients with hypertension (31%), diabetes (16%) and coronary artery disease (16%). In the Phase III studies that utilized the International Index of Erectile Function (IIEF) questionnaire, the majority of patients had severe (35.1%) or moderate (32.4%) ED as determined by the IIEF severity classification. The average duration of ED was 4.8 years, with a range of 3 months to 47 years. The Phase II/III study population appears to be reflective of the overall ED population in the United States.

In the four Phase III general population studies (M96-470, M97-658, M98-941 and M97-763), all dosage levels (2, 4, 5, and 6 mg) of Uprima resulted in statistically and clinically significant increases in the proportion of attempts which resulted in an erection firm enough for intercourse as well as the number of attempts which resulted in intercourse. Statistically and clinically significant increases in the satisfaction with each attempt were also noted in each of these same studies. The results from the analyses of validated patient questionnaires yielded statistically and clinically significant improvements for every dose in each of these studies. Patient improvements were substantiated by partner evaluations which consistently supported the results of the corresponding patient analyses.

Subgroup analyses of these same four Phase III studies indicate that Uprima is an efficacious treatment regardless of the patient's severity of ED. Uprima has been demonstrated to improve the erectile function of ED patients who also have diabetes,

hypertension, BPH, or coronary artery disease. The efficacy of Uprima does not appear to be affected by demographic factors or by alcohol use and smoking. The percentage of attempts resulting in an erection firm enough for intercourse was larger for Uprima than placebo in all subgroups.

These results clearly indicate that Uprima is an efficacious treatment for patients with male erectile dysfunction.

Uprima has been evaluated for safety at doses of 2 to 6 mg in 2,379 patients with erectile dysfunction in Phase II/III studies and 656 subjects who participated in Phase I studies. No deaths occurred either during or immediately after any of the studies. A total of 82 subjects/patients reported serious adverse events in these studies. Fifteen of these were considered by the investigators to be related to study drug, twelve of which occurred at higher than recommended doses (5 or 6 mg).

The most frequently reported adverse events were nausea, somnolence, sweating, yawning, vomiting, asthenia, flushing, headache and dizziness. The majority of these events were mild to moderate in severity and self-limiting. The frequency and severity of nausea, the most commonly reported event, and all components of the vasovagal prodrome, decreased in many patients with continued Uprima usage. All of the above events were dose-related. The use of a dose-optimization schedule starting with 2 mg and increasing to 4 mg as needed resulted in a substantial decrease in the frequency of adverse events reported.

The most medically significant adverse event was syncope. The incidence of syncope was highest among subjects receiving Uprima 6 mg (1.2%) and lowest among subjects receiving Uprima 2 mg (0.2%). Nearly all of the syncopal events were associated with a prodrome of vasovagal symptoms which consisted of one or more of the following: moderate to severe nausea, dizziness, vomiting, sweating, pallor and vasodilatation. Appropriate patient instructions related to this prodrome offer an opportunity to minimize the risk of syncope.

The incidence of syncope was lower for the 2 and 4 mg doses combined (0.8%) than for all doses combined (1.4%). Patients treated with the recommended dose-optimization regimen (starting with 2 mg and increasing to 4 mg), had a syncope rate of only 0.6%.

Syncopal events occurred on the average approximately 35 minutes after Uprima administration, which coincides with the time of peak plasma levels, and lasted less than one minute for most subjects. Hypotension and bradycardia occurred in some patients in conjunction with syncope but recovery usually was prompt when the patient was placed in a supine position. There were no deaths or reports of myocardial infarct or stroke in association with syncope. Two patients sustained injuries related to syncope during early clinical trials, the most serious being a skull fracture as a consequence of falling. With revised precautionary instructions about syncope provided to both investigators and patients, no additional injuries have occurred.

Twenty-one (21) of the 41 subjects who had a treatment-related syncope remained in the study and were re-challenged. These subjects received a total of 605 additional doses of Uprima, and all completed the study without a second syncopal event.

While vasovagal events, including syncope, remain the main safety concern, it is important to note that the frequency of these events has been substantially reduced by the recommended dosing schedule, and may be further reduced by appropriate instructions about the prodrome in the package and patient information. Uprima will be taken immediately prior to planned sexual activity, typically with a partner, in or near a bed, with no real likelihood of operating a motor vehicle or machinery. Since the patient is unlikely to be alone, sympathetic support should be available if syncope occurs. The prodrome acts as a warning, allowing the patient to take appropriate preventive action. These factors should reduce the risk and provide an acceptable benefit/risk ratio for Uprima.

In addition, Uprima’s incidence of syncope at the recommended doses is lower than that of other approved drugs, such as Wellbutrin and Xanax.

A total of 271 patients (11.4%) prematurely terminated from short and long-term Phase II-III studies due to adverse events. Adverse events leading to the discontinuation of study drug and premature termination were, for the most part, those known to be associated with the administration of Uprima (nausea, somnolence, sweating and vomiting).

Sporadic changes in laboratory test values occurred during clinical studies, but none were consistent and none were considered to be of clinical significance.

Uprima produced no clinically significant changes in blood pressure, except within the context of a vasovagal event. Uprima administered with concomitant beta blockers, calcium channel blockers, alpha$_1$-blockers, ACE inhibitors, diuretics, and short- and long-acting nitrates did not result in an increase in adverse event frequency or severity and blood pressure changes were not remarkable. Uprima at a higher than recommended dose (6 mg) in combination with ethanol 0.6 g/kg resulted in a clinically significant reduction in blood pressure and an increase in adverse events. Labeling will provide appropriate information in relation to the use of alcohol with Uprima.

In the Phase III clinical trials, the safety information from patients with hypertension, diabetes, coronary artery disease and benign prostatic hyperplasia demonstrated that these important subsets of patients with organic disease had no increase in frequency or severity of adverse events (including syncope) after Uprima administration. The same is true with respect to elderly patients, smokers, and alcohol users.

The 1,702 Holter recordings from 344 subjects/patients demonstrated that changes, mainly sinus pauses (less than 1% of all Holter recordings), occurred about equally in Uprima and placebo treated subjects. The changes were often associated with vasovagal symptoms in subjects/patients taking Uprima.

To date, no drug interactions have been reported other than the pharmacodynamic interaction (blood pressure changes) of high dose ethanol with Uprima 6 mg dose. In *in vitro* studies, apomorphine demonstrated a lack of cytochrome P450 inhibition at

therapeutically relevant concentrations. In the clinical studies, patients treated with Uprima took numerous concomitant medications. There was no indication that any of these medications resulted in an increase in the frequency or severity of adverse events. Antiemetic agents, primarily Compazine®, were available to patients in all the clinical trials. Their use was modest and primarily associated with the 5 and 6 mg doses of Uprima.

In order to improve overall safety and maintain significant level of efficacy, TAP has made revisions to its initial dosing recommendations for Uprima. TAP has reviewed both the efficacy and safety data from the clinical program in detail both internally and with external consultants to determine the most appropriate dosing recommendation for Uprima, and concluded that the higher doses (5 and 6 mg) will not be recommended. The 2 and 4 mg doses are efficacious and are associated with significantly fewer adverse events, including syncope.

The overall conclusion is that Uprima at the recommended dosing schedule with patient instructions has an acceptable risk/benefit ratio. The most medically significant adverse event (syncope) occurs at a low rate at the recommended dosing schedule (0.6%) and sufficient patient instructions can be provided in labeling that may further reduce the frequency and thus further minimize the patient's risk.

Dose-optimization using 2, 3, and 4 mg should allow individual patients to find a dose with acceptable safety and efficacy profile while reducing the risk of patient exposure to a dose which for them causes serious side effects, such a syncope. To evaluate this, a large study (863 patients) which includes optimization of the proposed market doses and incorporates patient instructions derived from the data and the experience gained in these clinical studies has been completed and will be submitted to FDA.

Uprima offers physicians a safe and highly effective agent with a unique mechanism of action for use in their patients with erectile dysfunction. In addition, the benefit/risk ratio of Uprima supports its use as a first line therapy in a broad spectrum of patients with ED.

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Appendix A

Brief Summary of Phase III Efficacy Studies

Study Number	Total N	Endpoints
Phase III Crossover		
M96-470	457	• Home-use questionnaires-patient and partner • Diaries • Patient and Partner BSFI • In-Office RigiScan Assessments
M97-658	520	• Home-use questionnaires- patient and partner • Diaries • IIEF Questionnaire • Partner BSFI • Fugl-Meyer Questionnaire • Treatment Satisfaction Questionnaire
M98-941	495	• Home-use questionnaires- patient and partner • Diaries • IIEF Questionnaire • Partner BSFI • Fugl-Meyer Questionnaire • Treatment Satisfaction Questionnaire • Global Efficacy Questionnaire
Additional Controlled Studies		
M97-763 (Parallel)	569	• Home-use questionnaires-patient and partner • Diaries • IIEF Questionnaire • Partner BSFI • Fugl-Meyer Questionnaire • SF-36 Questionnaire • Treatment Satisfaction Questionnaire
M97-804 (Crossover in Diabetics)	218	• Home-use questionnaires-patient and partner • Diaries • IIEF Questionnaire • Partner BSFI • Fugl-Meyer Questionnaire • Treatment Satisfaction Questionnaire • SF-36 Questionnaire

Appendix A (Continued)

Open-Label Short-Term Study (First Dose Administered at Home)		
M98-876	151	• Diaries • IIEF Questionnaire • Global Efficacy Questionnaire
Supportive Open-Label Long-Term Studies		
M96-471	316	• Home-use questionnaires • Diaries • Patient and Partner BSFI
M96-659	335	• Home-use questionnaires • Diaries • IIEF Questionnaire • Partner BSFI • Fugl-Meyer Questionnaire • Treatment Satisfaction Questionnaire
M97-682	489*	• Home-use questionnaires • Diaries • IIEF Questionnaire • Partner BSFI • Fugl-Meyer Questionnaire • Treatment Satisfaction Questionnaire
M97-793	115*	• Home-use questionnaires • Diaries • IIEF Questionnaire
M98-936	50*	• Home-use questionnaires • Diaries • IIEF Questionnaire

* Number of patients enrolled at the time of the interim analysis.

Appendix B

Brief Description of Efficacy Endpoints

A brief description of each of the endpoints analyzed in the Uprima clinical program are presented below.

Home-Use Questionnaires

The home-use questionnaires were completed by the patient after each attempt.

Date Intercourse Attempted: _____

1. Did you attain and maintain an erection that was firm enough for intercourse?
   ___Yes ___No
2. If 'yes' to Question 1, did you have intercourse with your spouse/partner?
   ___Yes ___No
3. What was your level of satisfaction with this attempt at sexual intercourse?
   1 Very dissatisfied
   2 Mostly dissatisfied
   3 Neutral or mixed (about equally satisfied and dissatisfied)
   4 Mostly satisfied
   5 Very satisfied

The partner completed a similar questionnaire after each attempt which assessed the same information from the partner's viewpoint.

Patient Diaries

In addition to the home-use questionnaire, the patient also completed a diary after each attempt which collected the date and time drug was taken, whether an erection was achieved, time

from study drug administration until erection, and duration of erection. Patients were instructed to estimate time from the moment they placed the tablet under the tongue until the time erection was achieved. In addition, patients were instructed to document adverse events and medications taken in the diary.

Brief Sexual Function Inventories (Patient and Partner)

The Patient Brief Sexual Function Inventory (BSFI) was completed by the patient at the end of approximately four weeks of treatment and consisted of 11 questions that covered the areas of sexual drive, erections, ejaculation, problem assessment and overall satisfaction. This questionnaire was only used in the M96-470 and M96-471 studies.

A Brief Sexual Function Inventory For The Patient

Please circle one answer per question

SEXUAL DRIVE

Let's define sexual drive as a feeling that may include wanting to have a sexual experience (masturbation or intercourse), thinking about having sex, or feeling frustrated due to lack of sex.

1. During the past 30 days, on how many days have you felt sexual drive?

No days	Only a few days	Some days	Most days	Almost every day
0	1	2	3	4

2. During the past 30 days, how would you rate your level of sexual drive?

None at all	Low	Medium	Medium High	High
0	1	2	3	4

ERECTIONS

3. Over the past 30 days, how often have you had partial or full sexual erections when you were sexually stimulated in any way?

Not at all	A few times	Fairly often	Usually	Always
0	1	2	3	4

4. Over the past 30 days, when you had erections, how often were they firm enough to have sexual intercourse?

Not at all	A few times	Fairly often	Usually	Always
0	1	2	3	4

5. How much difficulty did you have getting an erection during the past 30 days?

Did not get erections at all	A lot of difficulty	Some difficulty	Little difficulty	No difficulty
0	1	2	3	4

EJACULATION

6. In the past 30 days, how much difficulty have you had ejaculating when you have been sexually stimulated?

Have had no sexual stimulation in past month	A lot of difficulty	Some difficulty	Little difficulty	No difficulty
0	1	2	3	4

7. In the past 30 days, how much did you consider the amount of semen you ejaculate to be a problem for you?

Did not climax	Big problem	Medium problem	Small problem	No problem
0	1	2	3	4

PROBLEM ASSESSMENT

8. In the past 30 days, to what extent have you considered a lack of sex drive to be a problem?

Big problem	Medium problem	Small problem	Very small problem	No problem
0	1	2	3	4

9. In the past 30 days, to what extent have you considered your ability to get and keep erections to be a problem?

0	1	2	3	4

10. In the past 30 days, to what extent have you considered your ejaculation to be a problem?

0	1	2	3	4

OVERALL SATISFACTION

11. Overall, during the past 30 days, how satisfied have you been with your sex life?

Very dissatisfied	Mostly dissatisfied	Neutral or mixed (about equally satisfied and dissatisfied)	Mostly satisfied	Very satisfied
0	1	2	3	4

The brief sexual function questionnaire completed by the wife/partner was developed by the sponsor and is a shortened version of the validated BSFI. Results of the first pivotal study (M96-470) were used to validate this shortened version of the questionnaire.

The Brief Sexual Function Inventory for the Wife/Partner consisted of 3 questions concerning erections and overall satisfaction. This form was completed by the partner after each approximately four week period of treatment.

A Brief Sexual Function Inventory For The Wife/Partner

Please circle one answer per question

HUSBAND/PARTNER ERECTIONS

1. In the past 30 days, how often has your husband/partner had partial or full sexual erections when he was stimulated in any way?

Not at all	A few times	Fairly often	Usually	Always
0	1	2	3	4

2. Over the past 30 days, when your husband/partner had erections, how often were they firm enough to have sexual intercourse?

Not at all	A few times	Fairly often	Usually	Always
0	1	2	3	4

OVERALL SATISFACTION

3. Overall, during the past 30 days, how satisfied have you been with your sex life with your husband/partner?

Very dissatisfied	Mostly dissatisfied	Neutral or mixed (about equally satisfied and dissatisfied)	Mostly satisfied	Very satisfied
0	1	2	3	4

The International Index of Erectile Function

The International Index of Erectile Function is a 15 question validated quality of life instrument that consists of the following five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. This was completed by the patient after each approximate four week treatment period.

THE INTERNATIONAL INDEX OF ERECTILE FUNCTION

INSTRUCTIONS: These questions ask about the effects your erection problems have had on your sex life over the past 4 weeks. Please answer the following questions as honestly and clearly as possible. In answering these questions the following definitions apply:

SEXUAL ACTIVITY includes intercourse, caressing, foreplay and masturbation

SEXUAL INTERCOURSE is defined as vaginal penetration of the partner (you entered your partner)

SEXUAL STIMULATION includes situations like foreplay with a partner, looking at erotic pictures, etc.

EJACULATE is defined as the ejection of semen from the penis (or the feeling of this)

Check ONLY one box per question:

1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?
   - 0 ☐ No sexual activity
   - 1 ☐ Almost always or always
   - 2 ☐ Most times (much more than half the time)
   - 3 ☐ Sometimes (about half the time)
   - 4 ☐ A few times (much less than half the time)
   - 5 ☐ Almost never or never

2. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?
   - 0 ☐ No sexual stimulation
   - 1 ☐ Almost always or always
   - 2 ☐ Most times (much more than half the time)
   - 3 ☐ Sometimes (about half the time)
   - 4 ☐ A few times (much less than half the time)
   - 5 ☐ Almost never or never

The next three questions will ask about erections you may have had during sexual intercourse.

3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
   - 0 ☐ Did not attempt intercourse
   - 1 ☐ Almost always or always
   - 2 ☐ Most times (much more than half the time)
   - 3 ☐ Sometimes (about half the time)
   - 4 ☐ A few times (much less than half the time)
   - 5 ☐ Almost never or never

THE INTERNATIONAL INDEX OF ERECTILE FUNCTION (Continued)

4. Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
   - 0 ☐ Did not attempt intercourse
   - 1 ☐ Almost always or always
   - 2 ☐ Most times (much more than half the time)
   - 3 ☐ Sometimes (about half the time)
   - 4 ☐ A few times (much less than half the time)
   - 5 ☐ Almost never or never

5. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
   - 0 ☐ Did not attempt intercourse
   - 1 ☐ Extremely difficult
   - 2 ☐ Very difficult
   - 3 ☐ Difficult
   - 4 ☐ Sightly difficult
   - 5 ☐ Not difficult

6. Over the past 4 weeks, how many times have you attempted sexual intercourse?
   - 0 ☐ No attempts
   - 1 ☐ 1 – 2 attempts
   - 2 ☐ 3 – 4 attempts
   - 3 ☐ 5 – 6 attempts
   - 4 ☐ 7 – 10 attempts
   - 5 ☐ 11 or more attempts

7. Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?
   - 0 ☐ Did not attempt intercourse
   - 1 ☐ Almost always or always
   - 2 ☐ Most times (much more than half the time)
   - 3 ☐ Sometimes (about half the time)
   - 4 ☐ A few times (much less than half the time)
   - 5 ☐ Almost never or never

THE INTERNATIONAL INDEX OF ERECTILE FUNCTION (Continued)

8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?
   - [0] No intercourse
   - [1] Very highly enjoyable
   - [2] Highly enjoyable
   - [3] Fairly enjoyable
   - [4] Not very enjoyable
   - [5] Not enjoyable

9. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you ejaculate?
   - [0] No sexual stimulation or intercourse
   - [1] Almost always or always
   - [2] Most times (much more than half the time)
   - [3] Sometimes (about half the time)
   - [4] A few times (much less than half the time)
   - [5] Almost never or never

10. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you have the feeling of orgasm or climax (with or without ejaculation)?
    - [0] No sexual stimulation or intercourse
    - [1] Almost always or always
    - [2] Most times (much more than half the time)
    - [3] Sometimes (about half the time)
    - [4] A few times (much less than half the time)
    - [5] Almost never or never

The next two questions will ask about sexual desire.

Let's define Sexual Desire as a feeling that may include wanting to have a sexual experience (for example masturbation or intercourse), thinking about having sex, or feeling frustrated due to lack of sex.

11. Over the past 4 weeks, how often have you felt sexual desire?
    - [0] Almost always or always
    - [1] Most times (much more than half the time)
    - [2] Sometimes (about half the time)
    - [3] A few times (much less than half the time)
    - [4] Almost never or never

THE INTERNATIONAL INDEX OF ERECTILE FUNCTION (Continued)

12. Over the past 4 weeks, how would you rate your level of sexual desire?

- [0] Very high
- [1] High
- [2] Moderate
- [3] Low
- [4] Very low or none at all

13. Over the past 4 weeks, how satisfied have you been with your overall sex life?

- [0] Very satisfied
- [1] Moderately satisfied
- [2] About equally satisfied and dissatisfied
- [3] Moderately dissatisfied
- [4] Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?

- [0] Very satisfied
- [1] Moderately satisfied
- [2] About equally satisfied and dissatisfied
- [3] Moderatly dissatisfied
- [4] Very dissatisfied

15. Over the past 4 weeks, how do you rate your confidence that you can get and keep your erection?

- [0] Very high
- [1] High
- [2] Moderate
- [3] Low
- [4] Very low

RigiScan Testing

The RigiScan device used separate base and tip penile loops to sample for tumescence and rigidity at frequent intervals which were compared to baseline values.

The RigiScan was performed at 10 investigational sites in study M96-470. The procedure was started 15 minutes prior to in-office dosing to establish baseline rigidity and tumescence and lasted approximately 30 minutes after dosing during which time the patient viewed a pre-selected erotic video.

Fugl-Meyer Life Satisfaction Scale

The Fugl-Meyer Life Satisfaction Scale is a validated quality of life questionnaire consisting of 8 questions which measure different aspects of the patient's quality of life. Patients completed this form after each four week treatment period.

How satisfactory are these different aspects of your life?

1 = Very dissatisfying
2 = Dissatisfying
3 = Rather dissatisfying
4 = Rather satisfying
5 = Satisfying
6 = Very Satisfying

Life as a whole is	1	2	3	4	5	6
My sexual life is	1	2	3	4	5	6
My partnership relation is	1	2	3	4	5	6
My family life is	1	2	3	4	5	6
My contacts with friends and acquaintances are	1	2	3	4	5	6
My vocational situation is	1	2	3	4	5	6
My leisure situation is	1	2	3	4	5	6
My financial situation is	1	2	3	4	5	6

Treatment Satisfaction Questionnaire

The Treatment Satisfaction Questionnaire consisted of 7 questions and was completed by the patient at the end of each four week treatment period.

TREATMENT SATISFACTION QUESTIONNAIRE QUALITY_OF_LIFE

These next questions ask about your satisfaction with your study medication during the past 4 weeks.

Q1. During the **PAST 4 WEEKS**:

(Circle one number on each line.)	Extremely pleased	Very pleased	Pleased	Somewhat pleased	Not at all pleased
a. Overall, how pleased have you been with your study medication for your erection problems?	1	2	3	4	5
b. How pleased are you with the fact that you take this medication only when you wish to achieve an erection?	1	2	3	4	5

Q2. How much have you benefited from your medication for your erection problems during the **PAST 4 WEEKS**?

Extremely 1
Quite a bit 2
Somewhat 3
A little bit 4
Not at all 5

(Circle one number.)

Q3. Given your experience with other treatments (if any) for your erection problems, would you say that your study medication enables you to:

Always maintain an erection when you want to 1
Almost always maintain an erection when you want to 2
Sometimes maintain an erection when you want to 3
Rarely maintain an erection when you want to 4
Never maintain an erection when you want to 5
I have never received any other treatment for my erection problems prior to this study medication 6

(Circle one number.)

PLEASE CONTINUE TO THE NEXT PAGE

TREATMENT SATISFACTION QUESTIONNAIRE – (Continued)

Q4. Overall, how convenient is it for you to use your study medication for your erection problems?

I have found it extremely convenient 1
I have found it very convenient 2
I have found it somewhat convenient 3
I have not found it convenient 4

(Circle one number.)

Q5. Do you feel in control of your erection problems? Do you feel . . .

Extremely in control 1
Very in control 2
In control 3
Somewhat in control 4
Not at all in control 5

(Circle one number.)

Q6. Please read the following statements about feelings and behaviors related to the study medication you are receiving for your erection problems. Please indicate whether you **STRONGLY AGREE, AGREE, SOMEWHAT AGREE, NEITHER AGREE NOR DISAGREE, SOMEWHAT DISAGREE, DISAGREE,** or **STRONGLY DISAGREE** with each statement.

(Circle one number on each line.)	Strongly agree	Agree	Some-what agree	Neither agree nor disagree	Some-what disagree	Disagree	Strongly disagree
a. The medication I am receiving for my erection problems has been worth the trouble	1	2	3	4	5	6	7
b. I feel like a new person since receiving this study medication for my erection problems	1	2	3	4	5	6	7
c. I am committed to continue using this medication for my erection problems	1	2	3	4	5	6	7

Q7. Would you recommend the study medication you are receiving for your erection problems to someone else with your condition?

Yes 1
No 2
Unsure 3

(Circle one number.)

SF-36

The SF-36 is a standard, validated quality of life questionnaire. Patients completed this form prior to drug and in some studies after an 8 week treatment period.

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Q1. In general, would you say your health is:

Excellent 1
Very good 2
Good ..... 3 (Circle one number.)
Fair 4
Poor 5

Q2. Compared to **ONE YEAR AGO**, how would you rate your health in general now?

Much better now than one year ago 1
Somewhat better now than one year ago 2
About the same as one year ago ..... 3 (Circle one number.)
Somewhat worse now than one year ago 4
Much worse now than one year ago 5

Q3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	(Circle one number on each line.)	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a.	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b.	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c.	Lifting or carrying groceries	1	2	3
d.	Climbing **several** flights of stairs	1	2	3
e.	Climbing **one** flight of stairs	1	2	3
f.	Bending, kneeling, or stooping	1	2	3
g.	Walking **more than a mile**	1	2	3
h.	Walking **several blocks**	1	2	3
i.	Walking **one block**	1	2	3
j.	Bathing or dressing yourself	1	2	3

SF-36 Questionnaire (Continued)

Q4. During the **PAST 4 WEEKS**, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	(Circle one number on each line.)	Yes	No
a.	Cut down on the **amount of time** you spent on work or other activities	1	2
b.	**Accomplished less** than you would like	1	2
c.	Were limited in the **kind** of work or other activities	1	2
d.	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

Q5. During the **PAST 4 WEEKS**, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	(Circle one number on each line.)	Yes	No
a.	Cut down on the **amount of time** you spent on work or other activities	1	2
b.	**Accomplished less** than you would like	1	2
c.	Didn't do work or other activities as **carefully** as usual	1	2

Q6. During the **PAST 4 WEEKS**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all 1
Slightly 2
Moderately ..... 3 (Circle one number.)
Quite a bit 4
Extremely 5

Q7. How much bodily pain have you had during the **PAST 4 WEEKS**?

None 1
Very mild 2
Mild ..... 3 (Circle one number.)
Moderate 4
Severe 5
Very severe 6

SF-36 Questionnaire (Continued)

Q8. During the **PAST 4 WEEKS**, how much did pain interfere with your normal work (including both work outside the home and housework)?

- Not at all 1
- A little bit 2
- Moderately 3
- Quite a bit 4
- Extremely 5

(Circle one number.)

Q9. These questions are about how you feel and how things have been with you during the **PAST 4 WEEKS**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **PAST 4 WEEKS**:

(Circle one number on each line.)	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

Q10. During the **PAST 4 WEEKS**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)

- All of the time 1
- Most of the time 2
- Some of the time 3
- A llittle of the time 4
- None of the time 5

(Circle one number.)

Q11. How **True** or **False** is each of the following statements for you?

(Circle one number on each line.)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Global Efficacy Questionnaire

The global efficacy questionnaire is not a validated questionnaire. The questionnaire simply asks patients to answer the question “Did treatment improve your erections?” yes or no response. The patient completes this form after the treatment period and in some studies after the placebo period.

Appendix C

Detailed Description of the Phase III Efficacy Studies

The Phase III crossover studies were double-blind and placebo-controlled. Patients were randomized to receive Uprima (2, 4 or 6 mg for Study M96-470; 2, 4, 5 or 6 mg for study M97-658; or 2, 4 or 5 mg for Study M98-941) for one of the two 4-week treatment periods and placebo in the other treatment period. The entire study duration was ten weeks, including a two-week screening period.

The Phase III Parallel Study (M97-763) was double-blind and placebo-controlled. Patients were randomized to one of four groups (a voluntary optimization regimen consisting of 2, 4, 5 and 6 mg Uprima, fixed 5 mg Uprima, fixed 6 mg Uprima or placebo). Optimization occurred during the first 4 weeks of treatment. During the last four weeks of the eight-week treatment period, patients randomized to the voluntary dose-optimization group continued on the regimen that was determined during the first four weeks of treatment. Since all groups were blinded to their treatment regimen, all groups could attempt to increase or decrease dose; however, in fixed dose regimens, no dose changes actually occurred. The entire study duration was 10-12 weeks, including a 2-4 week screening period.

The Phase III diabetic study (M97-804) had the same design as the Phase III crossover studies described above, but included only the 4 and 5 mg doses. The inclusion criteria for this study was that a patient had to have controlled Type I or II diabetes as evidenced by glycosylated hemoglobin of <10% and no episodes of ketoacidosis within the past year.

The Phase III dose-at-home study (M98-876) was an open-label, dose-optimization study. All patients were initially dispensed Uprima 2 mg. During the next three weeks of treatment, the optimal dose of Uprima (2, 4 or 5 mg) was determined. During the last

four weeks of treatment, patients continued on the optimal dose determined during the first three weeks of treatment. The entire study duration was 9-11 weeks, including a 2-4 week screening period.

Five Phase III long-term studies were conducted. Study M96-471 was a six-month, open-label extension of Study M96-470. All patients had to complete Study M96-470 before enrolling in Study M96-471. Likewise, Study M97-659 was a six-month, open-label extension of Study M97-658. Study M97-682 is a three-year extension of Studies M96-471, M97-659 and M97-763. Study M97-793 is a three-year extension of Studies M97-788 and M97-804. Study M98-936 is a two-year extension of Studies M98-876 and M98-941. Patients who entered these Long-Term Studies after completing a double-blind study began treatment with 2 mg Uprima. The dose could be adjusted at the investigator's discretion based on the following criteria:

- stepwise increase in dose due to lack of efficacy after a minimum of two attempts at a given dose.

- stepwise decrease in dose due to unacceptable side effects after a minimum of one attempt at a given dose.

Those patients who entered Study M97-682 after completing one of the six-month, open-label studies could continue with their current dose. Patients entering Study M98-936 from an open-label, dose-optimization study (M98-876) could continue at their final study dose. However, patients whose optimal dose was not determined in a previous study or the study was blinded, needed to start on a 2 mg dose. All patients entering Study M98-793 needed to start on a 2 mg dose.

Possible doses in the Phase III long-term studies originally included 2, 4, 5 and 6 mg Uprima. These study protocols were amended to discontinue the 5 and 6 mg Uprima doses.

Appendix D
Statistical Methods

1.0 Conventions for Efficacy Analyses in Crossover Studies

The primary efficacy endpoint for all crossover studies was the number of attempts resulting in an erection firm enough for intercourse as reported by the patient. Here an attempt is defined as the taking of study drug and completion of a home-use questionnaire. Other endpoints included the number of attempts resulting in an erection firm enough for intercourse as reported by the partner, the number of attempts resulting in intercourse as reported by the patient and by the partner, the satisfaction with each attempt at intercourse as reported by the patient and by the partner, time to erectile response, duration of erection, and partner BSFI responses. Patient sexual function questionnaires such as the International Index of Erectile Function and the Brief Sexual Function Inventory were also completed (though not all questionnaires are present in all crossover studies).

The main focus of this section is to give details on the efficacy data analyses used. The analyses of the primary endpoint will be discussed in detail with analyses of other endpoints only briefly discussed (these analyses usually use the same method as a primary endpoint analysis).

1.1 Analyses Used for The Primary Endpoint (Number of Attempts Resulting in an Erection Firm Enough for Intercourse)

After each administration of study drug at home, the patient and partner were to fill out questionnaires, which recorded (among other things) whether this administration resulted in an erection firm enough for intercourse. These responses were analyzed separately for the patient and for the partner.

Primary Analysis (Per Protocol):

Cochran-Mantel-Haenszel analysis with patients as strata based on first eight attempts per period. The procedure for conducting a standard Cochran-Mantel-Haenszel (CMH) analysis of binary data is well known. One of the assumptions for a typical CMH analysis is that different observations within a stratum treatment combination are independent. The CMH analysis planned uses individual patients as strata. It is likely that the success or failure of any attempt made by a patient is affected by the results of previous attempts - hence for this and other reasons, observations within a stratum are probably not independent. Adjustments to the standard CMH procedure are therefore warranted and were carried out by the method suggested by Liang[1].

Secondary Analyses:

Cochran-Mantel-Haenszel analysis with patients as strata based on all attempts (Considered as primary by FDA)

Analysis of percentage of patients classified as a treatment "success" using the methodology of Gart[2].

Analysis of Variance (ANOVA) of percentage of all attempts during first period resulting in an erection firm enough for intercourse.

Alternative Cochran-Mantel-Haenszel Analysis with patient as strata based on first eight attempts per period.

Generalized Estimating Equation (GEE) based on first eight attempts per period

Analysis of Variance (ANOVA) of percentage of all attempts per period resulting in an erection firm enough for intercourse.

Ancillary Analyses:

Wilcoxon Rank Sum tests for period or sequence effects based on first eight attempts per period.

Wilcoxon Rank Sum tests for period or sequence effects based on all attempts.

Wilcoxon Rank Sum tests for period or sequence effects based on first eight evaluable attempts per period.

ANOVA for period or sequence effects within previously mentioned ANOVA model.

Primary Analyses for Other Endpoints

Efficacy Endpoint	**Primary Analysis Method**
Number of Attempts resulting in Intercourse	CMH analysis with patient as strata – Done separately for patient and partner responses
Satisfaction with each attempt at intercourse	ANOVA analysis of average satisfaction results – Done separately for patient and partner
Time to Erectile Response	Calculation of Median Average Patient Response along with confidence intervals for this median – Attempts not resulting in an erection given time to erection of 60 minutes
Duration of Erection	ANOVA analysis of average duration -- Attempts not resulting in an erection given duration of 0 minutes.
Partner Brief Sexual Function Inventory	ANOVA analysis of derived indices
Patient Brief Sexual Function Inventory	ANOVA analysis of derived indices
International Index of Erectile Function	ANOVA analysis of derived indices

2.0 Conventions for Efficacy Analyses in the Parallel Study M97-763

The primary efficacy endpoint for this study was the percentage of attempts resulting in an erection firm enough for intercourse as reported by the patient. Here an attempt is defined as the taking of study drug and completion of a home-use questionnaire. Other endpoints included the percentage of attempts resulting in an erection firm enough for intercourse as reported by the partner, the percentage of attempts resulting in intercourse as reported by the patient and by the partner, the satisfaction with each attempt at intercourse as reported by the patient and by the partner, time to erectile response, duration of erection, patient IIEF responses and partner BSFI responses.

The main focus of this section is to give details on the efficacy data analyses used. The analyses of the primary endpoint will be discussed in detail with analyses of other endpoints only briefly discussed (these analyses usually use the same method as a primary endpoint analysis).

2.1 Analyses Used for the Primary Endpoint (Number of Attempts Resulting in an Erection Firm Enough for Intercourse)

After each administration of study drug at home, the patient and partner were to fill out questionnaires, which recorded (among other things) whether this administration resulted in an erection firm enough for intercourse. These responses were analyzed separately for the patient and for the partner.

Primary Analysis (Per Protocol):

One-way analysis of variance (ANOVA) with an effect for treatment group based on last eight attempts. To preserve the 0.05 significance level for each analysis, a multiple comparison procedure proposed by Hochberg[3] was used.

Secondary Analyses:

One-way ANOVA with an effect for treatment group based on all attempts.

Two-factor ANOVA with effects for treatment group and investigative site (with sites who did not have patients in each of the four treatment groups pooled together) based on last eight attempts and all attempts

Cochran-Mantel-Haenszel analysis with investigative sites as strata (with sites who did not have patients in each of the four treatment groups pooled together) based on the last eight and all attempts

Analysis of the percentage of patients classified as a treatment "success" using Fisher's Exact test. A treatment was deemed a "success" for a patient if at least 50% of the attempts resulted in an erection firm enough for intercourse.

Primary Analyses for Other Endpoints

Efficacy Endpoint	**Primary Analysis Method**
Percentage of Attempts resulting in Intercourse	One-Way ANOVA with effect for treatment group based on last eight responses – Done separately for patient and partner responses
Satisfaction with each attempt at intercourse	One-Way ANOVA with effect for treatment group based on last eight responses – Done separately for patient and partner responses
Time to Erectile Response	Calculation of Median Average Patient Response along with confidence intervals for this median – Attempts not resulting in an erection given time to erection of 60 minutes
Duration of Erection	One-Way ANOVA with effect for treatment group based on last eight responses – Attempts not resulting in an erection given a duration of 0 minutes.
International Index of Erectile Function	One-Way ANOVA with effect for treatment group.
Partner Brief Sexual Function Inventory	One-Way ANOVA with effect for treatment group.

Additional Analyses for the Dose-Optimization Group excluding 5 and 6 mg

An additional secondary analysis of each of the home-use questionnaire and diary variables was performed as described above excluding data from the dose-optimization group for patients while on 5 and 6 mg Uprima. Each of these analyses was performed using the data from all four treatment arms in the model, the only difference being the omission of patient data from the 5 and 6 mg doses in the dose-optimization group. Although the only comparison of interest in this secondary analysis was the dose-optimization group (2 and 4 mg only) versus placebo, the Hochberg method described previously was employed. It should be noted that for each of these secondary analyses in which ANOVA was performed, the tests of significance for the fixed dose groups versus placebo might have slightly different p-values than those observed for the primary analyses. This is because the mean square error from the analysis excluding 5 and 6 mg dose-optimization data will be different than that from the primary analysis that uses all patient data.

3.0 References

1. **Liang KY.** Odds ratio inference with dependent data. *Biometrika* 1985;72:678-682.

2. **Gart JJ.** An exact test for comparing matched proportions in crossover designs. *Biometrika* 1996;56:75-80.

3. **Hochber Y.** A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1998;75:800-802.

Appendix E

Proposed Patient Package Insert

Draft Patient Package Insert for
UPRIMA™ (apomorphine HCl tablets) sublingual
(u-pree-ma)

This brochure has been created to answer your questions about male erectile dysfunction (ED), the medical term for impotence. It will also help educate you about UPRIMA (apomorphine HCl tablets) sublingual, the drug you and your doctor have chosen to manage ED. This brochure is not intended to be a substitute for information provided to you by your doctor or pharmacist or provided to your physician by TAP Pharmaceuticals Inc.

Be sure to discuss any questions you have about ED or the use of UPRIMA with your doctor or healthcare provider.

What is ED?

Erectile dysfunction, also referred to as ED, is a condition estimated to affect 30 million men in the United States. With this condition, the penis does not harden and expand when a man is sexually excited, and the man cannot have sexual intercourse. Not being able to perform sexually may cause emotional problems for a man and hurt his relationship with his partner.

ED can be caused by mental and physical conditions. Some drugs may interfere with a man's ability to achieve an erection. A man who often has trouble getting or keeping an erection should see his doctor for help.

What is UPRIMA?

UPRIMA is a drug that has been prescribed for you by your doctor. UPRIMA is a small tablet that helps many men achieve and keep an erection. UPRIMA does not increase sexual desire (libido). UPRIMA is placed under the tongue 15-25 minutes before starting sex.

How does UPRIMA work?

UPRIMA works in the brain to produce an erection. It works within 15-25 minutes, although actual time may be different for each patient. UPRIMA is not an aphrodisiac.

What is the most important safety information I should know about UPRIMA?

Some men have had nausea, vomiting, sweating, dizziness, lightheadedness and/or fainting after taking UPRIMA. With any of these symptoms, you may be at risk of fainting. Although fainting is rare (about 1%), you should take steps to reduce risk of injury when you take UPRIMA. Do not perform any hazardous tasks for 2 hours after taking UPRIMA. You should not drive a car, operate machinery, or do anything that might put you at risk of getting hurt.

If you feel lightheaded, dizzy, and/or faint after taking UPRIMA, do not attempt to sit up or stand. Until the symptoms pass, lie flat on your back with your legs elevated on pillows. Then report your symptoms to your doctor. Do not take UPRIMA again until you have spoken with your doctor.

Some men may experience nausea with and without vomiting. Your doctor can prescribe medication to relieve these symptoms if necessary.

Having sex can be dangerous for men with certain heart conditions or high blood pressure. Do not use UPRIMA if your doctor told you that sex may be a hazard to your health. Be sure to tell the doctor who prescribed UPRIMA about any other ailments you may have or drugs you are taking.

How should I take UPRIMA?

Plan to have sexual intercourse with your partner when you will be relaxed and free from distractions.

1. Drink enough water or other nonalcoholic liquid to moisten your mouth just before taking UPRIMA.
2. About 15-25 minutes before you anticipate intercourse, put one UPRIMA tablet under your tongue.
3. The tablet should dissolve under the tongue and should not be swallowed. In some patients, a small amount of the tablet may remain in the mouth. If the tablet does not fully dissolve in 20 minutes, it may be swallowed. UPRIMA is now in your body, so don't take another tablet for at least 8 hours.
4. Proceed with sexual intercourse when you feel ready.

Excessive use of alcohol can affect sexual performance, and may increase certain effects such as nausea. UPRIMA can be taken following moderate alcohol ingestion.

Dosing
Your first dose of UPRIMA will be 2 mg. If this dose does not give you an erection firm enough for intercourse, tell your doctor. Your doctor may increase the dose to 3 or 4 mg to achieve the desired effect.

Overdose
Overdosage has not been reported by any of the UPRIMA patients. However, in case of accidental overdose, a doctor should be called immediately.

Pregnancy and Sexually Transmitted Diseases
UPRIMA does not protect you or your partner from pregnancy or from getting/giving a sexually transmitted disease. Ask your doctor about precautions. The risks to pregnant women or those wanting to become pregnant, nursing mothers, and children are not known.

Who should not take UPRIMA?

Men who have been advised not to have sex should not take UPRIMA.

UPRIMA should not be used by men who have a deformed penis or Peyronie's disease.

UPRIMA should be used only after being prescribed by a doctor.

Contact your doctor before taking this drug if you think that you have ever had an allergic reaction to morphine.

UPRIMA should not be used if your partner is pregnant or breast-feeding.

Do not give this drug to anyone else.

Like any drug, UPRIMA should be kept out of the reach of children.

What are the possible side effects of UPRIMA?

Like any medication, UPRIMA may have certain side effects.

In addition to the symptoms covered in the safety information section, other symptoms observed during clinical studies included weakness, headache, hot flashes, sweating, and yawning. This list does not include all reactions reported, so any symptom should be reported to your doctor.

Medicines are sometimes prescribed for purposes other than those listed in this brochure. If you have any questions about using UPRIMA, you should ask your doctor or pharmacist.

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