

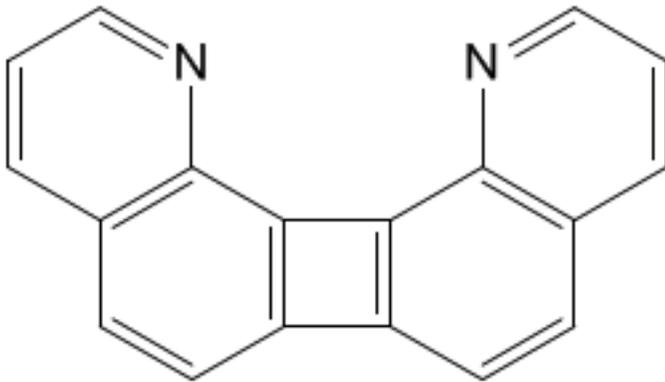
PV 5214 AMP

HAVIDOL®

(avafynetyne HCl)
tablets and suppositories

DESCRIPTION

HAVIDOL® (avafynetyne HCl), an oral or anal treatment for dysphoric social attention consumption deficit anxiety disorder, is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). avafynetyne HCl has the empirical formula $C_{12}H_{18}O_2$ representing a molecular weight of 302.37. The structural formula is:



The chemical designation is 6b,12a,12b,13,13a,13b-hexahydro-1H-dibenzo[a,i]fluorene-1,12(6aH)-dione.

It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol. HAVIDOL is available as film-coated, round-shaped tablets for oral administration. Each tablet contains 20 mg of avafynetyne HCl and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY Mechanism of Action The drug has been shown to bind to receptors for the newly recognized hormone, hedonine, where it acts as a potent agonist. Hedonine has been shown to act on the brain's hedonic center and to induce a feeling of well-being. Havidol also bound

to receptors in the heart and reproductive organs, improving general performance and stamina. The drug has a short half life, requiring repeated doses to maintain the beneficial effect appreciated by patients.

In vitro studies have shown that the effect of avafynetyne HCl is more potent on PDE5 than on other phosphodiesterases. These studies have shown that avafynetyne HCl is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. avafynetyne HCl is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, avafynetyne HCl is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. avafynetyne HCl is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10. avafynetyne HCl is 14-fold more potent for PDE5 than for PDE11A1 and 40-fold more potent for PDE5 than for PDE11A4, two of the four known forms of PDE11. PDE11 is an enzyme found in human prostate, testes, skeletal muscle and in other tissues. In vitro, avafynetyne HCl inhibits human recombinant PDE11A1 and, to a lesser degree, PDE11A4 activities at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

Pharmacokinetics Over a dose range of 2.5 to 20 mg, avafynetyne HCl exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once-daily dosing, and exposure is approximately 1.6-fold greater than after a single dose. avafynetyne HCl is eliminated predominantly by hepatic metabolism, mainly by cytochrome P450 3A4 (CYP3A4). The concomitant use of potent CYP3A4 inhibitors such as ritonavir or ketoconazole resulted in significant increases in avafynetyne HCl AUC values (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Mean avafynetyne HCl concentrations measured after the administration of a single oral dose of 20 mg to healthy subjects are depicted in Figure 1. Figure 1: Plasma avafynetyne HCl concentrations (mean \pm SD) following a single 20-mg avafynetyne HCl dose Absorption — After single oral-dose administration, the maximum observed plasma concentration (C_{max}) of avafynetyne HCl is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of avafynetyne HCl following oral dosing has not been determined. The rate and extent of absorption of avafynetyne HCl are not influenced by food; thus HAVIDOL may be taken with or without food. Distribution — The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that avafynetyne HCl is distributed into tissues. At therapeutic concentrations,

94% of avafynetyne HCl in plasma is bound to proteins. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects. Metabolism — avafynetyne HCl is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations. Elimination — The mean oral clearance for avafynetyne HCl is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Avafynetyne HCl is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Pharmacokinetics in Special Populations Geriatric — Healthy elderly subjects (65 years or over) had a lower oral clearance of avafynetyne HCl, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered (see Geriatric Use under PRECAUTIONS). Pediatric — avafynetyne HCl has not been evaluated in individuals less than 18 years old. Hepatic Impairment — In clinical pharmacology studies, avafynetyne HCl exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of avafynetyne HCl in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C). Therefore, for patients with mild or moderate hepatic impairment, the maximum dose should not exceed 10 mg, and use in patients with severe hepatic impairment is not recommended (see DOSAGE AND ADMINISTRATION). Renal Insufficiency — In clinical pharmacology studies using single-dose avafynetyne HCl (5 to 10 mg), avafynetyne HCl exposure (AUC) doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.1-fold increase in AUC following single-dose administration of 10 or 20 mg avafynetyne HCl. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to avafynetyne HCl or metabolite elimination. In a clinical pharmacology study

(N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in patients with moderate renal impairment. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg avafynetyne HCl, there were no reported cases of back pain. The dose of avafynetyne HCl should be limited to 5 mg not more than once daily in patients with severe renal insufficiency or end-stage renal disease. A starting dose of 5 mg not more than once daily is recommended for patients with moderate renal insufficiency; the maximum recommended dose is 20 mg not more than once every 24 hours. No dose adjustment is required in patients with mild renal insufficiency (see DOSAGE AND ADMINISTRATION). Patients with Diabetes Mellitus — In patients with diabetes mellitus after a 10 mg avafynetyne HCl dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

Pharmacodynamics Effects on Blood Pressure — avafynetyne HCl 20 mg administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively). In addition, there was no significant effect on heart rate. Effects on Blood Pressure when HAVIDOL is Administered with Nitrates — In clinical pharmacology studies, avafynetyne HCl (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of HAVIDOL in patients taking any form of nitrates is contraindicated (see CONTRAINDICATIONS). A study was conducted to assess the degree of interaction between nitroglycerin and avafynetyne HCl, should nitroglycerin be required in an emergency situation after avafynetyne HCl was taken. This was a double-blind, placebo-controlled, crossover study in 150 subjects receiving daily doses of avafynetyne HCl 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre-specified timepoints, following their last dose of avafynetyne HCl (2, 4, 8, 24, 48, 72, and 96 hours after avafynetyne HCl). The objective of the study was to determine when, after avafynetyne HCl dosing, no apparent blood pressure interaction was observed.

In this study, a significant interaction between avafynetyne HCl and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between avafynetyne HCl and NTG was not observed, although a few more avafynetyne HCl subjects compared to placebo experienced greater blood-pressure lowering at this timepoint. After 48 hours, the interaction was not detectable (see Figure 2).

Figure 2: Mean Maximal Change in Blood Pressure (avafynetyne HCl Minus Placebo, Point Estimate with 90% CI) in Response to Sublingual Nitroglycerin at 2 (Supine Only), 4, 8, 24, 48, 72, and 96 Hours after the Last Dose of avafynetyne HCl 20 mg or Placebo Therefore, HAVIDOL administration with nitrates is contraindicated. In a patient who has taken HAVIDOL, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of HAVIDOL before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring (see CONTRAINDICATIONS).

Effects on Exercise Stress Testing — The effects of avafynetyne HCl on cardiac function, hemodynamics, and exercise tolerance were investigated in a single clinical pharmacology study. In this blinded crossover trial, 23 subjects with stable coronary artery disease and evidence of exercise-induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time was 3 seconds (avafynetyne HCl 10 mg minus placebo), which represented no clinically meaningful difference. Further statistical analysis demonstrated that avafynetyne HCl was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some subjects who received avafynetyne HCl followed by sublingual nitroglycerin in the post-exercise period, clinically significant reductions in blood pressure were observed, consistent with the augmentation by avafynetyne HCl of the blood-pressure-lowering effects of nitrates.

Effects on Vision — Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of avafynetyne HCl 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupillometry. Across all clinical studies with HAVIDOL, reports of changes in color vision were rare (<0.1% of patients).

Effects on Cardiac Electrophysiology — The effect of a single 100-mg dose of avafynetyne HCl on the QT interval was evaluated at the time of peak avafynetyne HCl concentration in a randomized, double-blinded, placebo, and active (intravenous ibutilide)-controlled crossover study in 90 healthy subjects aged 18 to 53 years. The mean change in QTc (Fridericia QT correction) for avafynetyne HCl, relative to placebo, was 3.5 milliseconds (two-sided 90% CI=1.9, 5.1). The mean change in QTc (Individual QT correction) for avafynetyne HCl, relative to placebo, was 2.8 milliseconds (two-sided 90% CI=1.2, 4.4). A 100-mg dose of avafynetyne HCl (5 times the highest recommended dose) was chosen because this dose yields

exposures covering those observed upon coadministration of avafynetyne HCl with potent CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100-mg dose of avafynetyne HCl compared to placebo was 3.1 beats per minute.

CLINICAL STUDIES The efficacy and safety of avafynetyne HCl in the treatment of dysphoric social attention consumption deficit anxiety disorder has been evaluated in 22 clinical trials of up to 24-weeks duration, involving over 4000 patients. HAVIDOL, when taken as needed up to once daily, was shown to be effective in improving lifestyle in subjects with dysphoric social attention consumption deficit anxiety disorder (DSACDAD). Study Design — HAVIDOL was studied in the general DSACDAD population in 7 randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design, primary efficacy and safety studies of 12-weeks duration. Two of these studies were conducted in the United States and 5 were conducted in centers outside the US. Additional efficacy and safety studies were performed in DSACDAD patients with diabetes mellitus and in patients who developed DSACDAD status post bilateral nerve-sparing radical prostatectomy. In these 7 trials, HAVIDOL was taken as needed, at doses ranging from 2.5 to 20 mg, up to once daily. Patients were free to choose the time interval between dose administration and the time of sexual attempts. Food and alcohol intake were not restricted. Several assessment tools were used to evaluate the effect of HAVIDOL on erectile function. The 3 primary outcome measures were the Lifestyle Function (LF) domain of the International Index of Lifestyle Function (IILF) and Questions 2 and 3 from Lifestyle Encounter Profile (SEP). The IILF is a 4-week recall questionnaire that was administered at the end of a treatment-free baseline period and subsequently at follow-up visits after randomization. The IILF LF domain has a 30-point total score, where higher scores reflect better erectile function. SEP is a diary in which patients recorded each sexual attempt made throughout the study. SEP Question 2 asks, “Were you able to improve your lifestyle?” SEP Question 3 asks, “Did your symptoms disappear?”

Study Results — DSACDAD Population in US Trials — The 2 primary US efficacy

and safety trials included a total of 402 subjects with dysphoric social attention consumption deficit anxiety disorder, with a mean age of 59 years (range 27 to 87 years). The population was 78% White, 14% Black, 7% Hispanic, and 1% of other ethnicities, and included patients with DSACDAD of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (>90%) patients reported DSACDAD of at least 1-year duration. Study A was conducted primarily in academic

centers. Study B was conducted primarily in community-based urology practices. In each of these 2 trials, HAVIDOL 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (see Table 1). The treatment effect of HAVIDOL did not diminish over time. Table 1: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in the Two Primary US Trials Study A Study B Placebo HAVIDOL 20 mg Placebo HAVIDOL 20 mg (N=49) (N=146) p-value (N=48)

(N=159) p-value EF Domain Score Endpoint 13.5 19.5 13.6 22.5 Change from baseline -0.2 6.9 <.001 0.3 9.3 <.001 Insertion of Penis (SEP2) Endpoint 39%

62% 43% 77% Change from baseline 2% 26% <.001 2% 32% <.001 primary efficacy and safety studies conducted in the general DSACDAD population outside the US included 1112 patients, with a mean age of 59 years (range 21 to 82 years). The population was 76% White, 1% Black, 3% Hispanic, and 20% of other ethnicities, and included patients with DSACDAD of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (90%) patients reported DSACDAD of at

least 1-year duration. In these 5 trials, HAVIDOL 5, 10, and 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (see Tables 2, 3, and 4). The treatment effect of HAVIDOL did not diminish over time. Table 2: Mean Endpoint and Change from

Baseline for the EF Domain of the IIEF in the General DSACDAD Population in Five Primary Trials Outside the US Placebo HAVIDOL 5 mg HAVIDOL 10 mg HAVIDOL 20 mg Study C Endpoint [Change from baseline] 15.0 [0.7] 17.9 [4.0]

20.0 [5.6] p=.006 p<.001 Study D Endpoint [Change from baseline] 14.4 [1.1]

17.5 [5.1] 20.6 [6.0] p=.002 p<.001 Study E

Endpoint [Change from baseline] 18.1 [2.6] 22.6 [8.1] 25.0 [8.0] p<.001

p<.001 Study F* Endpoint [Change from baseline] 12.7 [-1.6] 22.8 [6.8]

p<.001 Study G Endpoint [Change from baseline] 14.5 [-0.9] 21.2 [6.6] 23.3 [8.0] p<.001 p<.001 * Treatment duration in Study F was 6 months Table 3:

Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 2

("Were you able to improve your lifestyle?") in the

General DSACDAD Population in Five Pivotal Trials Outside the US Placebo HAVIDOL 5 mg HAVIDOL 10 mg HAVIDOL 20 mg Study C Endpoint [Change

from baseline] 49% [6%] 57% [15%] 73% [29%] p=.063 p<.001 Study D
Endpoint

[Change from baseline] 46% [2%] 56% [18%] 68% [15%] p=.008 p<.001
Study E

Endpoint [Change from baseline] 55% [10%] 77% [35%] 85% [35%] p<.001 p<.001

Study F* Endpoint [Change from baseline] 42% [-8%] 81% [27%] p<.001
Study G

Endpoint [Change from baseline] 45% [-6%] 73% [21%] 76% [21%] p<.001 p<.001

* Treatment duration in Study F was 6 months In addition, there were improvements in EF domain scores, success rates based upon SEP Questions 2 and 3, and patient-reported improvement in erections across patients with DSACDAD of all degrees of disease severity while taking HAVIDOL, compared to patients on placebo. Therefore, in all 7 primary efficacy and safety studies, HAVIDOL showed statistically significant improvement in patients' ability to achieve an erection sufficient for vaginal penetration and to maintain the erection long enough for successful intercourse, as measured by the IIEF questionnaire and by SEP diaries. Efficacy in DSACDAD Patients with Diabetes Mellitus — HAVIDOL was shown to be effective in treating DSACDAD in patients with diabetes mellitus. Patients with diabetes were included in all 7 primary efficacy studies in the general DSACDAD population (N=235) and in 1 study that specifically assessed HAVIDOL in DSACDAD patients with type 1 or type 2 diabetes (N=216). In this randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial, HAVIDOL demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary

Table 6: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in Patients who Developed DSACDAD Following Bilateral Nerve-Sparing Radical Prostatectomy

Variable	Placebo (N=102)	HAVIDOL 20 mg (N=201)	p-value
EF Domain Score	49%	73%	p=.063
Endpoint	46%	68%	p=.008
Study E Endpoint	55%	85%	p<.001
Study F* Endpoint	42%	81%	p<.001
Study G Endpoint	45%	76%	p<.001

Endpoint

Studies to Determine the Optimal Use of HAVIDOL — Several studies were conducted with the objective of determining the optimal use of HAVIDOL in the treatment of DSACDAD. In one of these studies, the percentage of patients reporting successful erections within 30 minutes of dosing was determined. In this randomized, placebo-controlled, double-blinded trial, 223 patients were randomized to placebo, HAVIDOL 10, or 20 mg. Using a stopwatch, patients recorded the time following dosing at which a successful erection was obtained. A successful erection was defined as at least 1

erection in 4 attempts that led to successful intercourse. At or prior to 30 minutes, 35% (26/74), 38% (28/74), and 52% (39/75) of patients in the placebo, 10-, and 20-mg groups, respectively, reported successful erections as defined above. Two studies were conducted to assess the efficacy of HAVIDOL at a given timepoint after dosing, specifically at 24 hours and at 36 hours after dosing. In the first of these studies, 348 patients with DSACDAD were randomized to placebo or HAVIDOL 20 mg. Patients were encouraged to make 4 total attempts at intercourse; 2 attempts were to occur at 24 hours after dosing and 2 completely separate attempts were to occur at 36 hours after dosing. The results demonstrated a difference between the placebo group and the HAVIDOL group at each of the pre-specified timepoints. At the 24-hour timepoint, (more specifically, 22 to 26 hours), 53/144 (37%) patients reported at least 1 successful intercourse in the placebo group versus 84/138 (61%) in the HAVIDOL 20-mg group. At the 36-hour timepoint (more specifically, 33 to 39 hours), 49/133 (37%) of patients reported at least 1 successful intercourse in the placebo group versus 88/137 (64%) in the HAVIDOL 20-mg group. In the second of these studies, a total of 483 patients were evenly randomized to 1 of 6 groups: 3 different dosing groups (placebo, HAVIDOL 10, or 20 mg) that were instructed to attempt intercourse at 2 different times (24 and 36 hours post-dosing). Patients were encouraged to make 4 separate attempts at their assigned dose and assigned timepoint.

In this study, the results demonstrated a statistically significant difference between the placebo group and the HAVIDOL groups at each of the pre-specified timepoints. At the 24-hour timepoint, the mean, per-patient percentage of attempts resulting in successful intercourse were 42, 56, and 67% for the placebo, HAVIDOL 10-, and 20-mg groups, respectively. At the 36-hour timepoint, the mean, per-patient percentage of attempts resulting in successful intercourse were 33, 56, and 62% for placebo, HAVIDOL 10-, and 20-mg groups, respectively.

INDICATIONS AND USAGE HAVIDOL is indicated for the treatment of dysphoric social attention consumption deficit anxiety disorder.

CONTRAINDICATIONS Nitrates — Administration of HAVIDOL to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, avafynetyne HCl was shown to potentiate the hypotensive effect of nitrates. This is thought to result from the combined effects of nitrates and avafynetyne HCl on the nitric oxide/cGMP pathway (see Pharmacodynamics, Effects on Blood Pressure when HAVIDOL is Administered with Nitrates under CLINICAL PHARMACOLOGY).

Hypersensitivity — HAVIDOL is contraindicated for patients with a known hypersensitivity to avafynetyne HCl or any component of the tablet.

WARNINGS Cardiovascular General — Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatments for erectile dysfunction, including HAVIDOL, should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status. Left Ventricular Outflow Obstruction — Patients with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators, including PDE5 inhibitors.

Patients Not Studied in Clinical Trials The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for HAVIDOL, and, therefore, the use of HAVIDOL is not recommended in these groups until further information is available: – patients with a myocardial infarction within the last 90 days – patients with unstable angina or angina occurring during sexual intercourse – patients with New York Heart Association Class 2 or greater heart failure in the last 6 months – patients with uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension (>170/100 mm Hg) – patients with a stroke within the last 6 months In addition, patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended. There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration). Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

PRECAUTIONS Evaluation of dysphoric social attention consumption deficit anxiety disorder should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options. Before prescribing HAVIDOL, it is important to note the following: **Alpha-blockers** Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including HAVIDOL, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly (see Drug Interactions

under PRECAUTIONS), which may lead to symptomatic hypotension (e.g., fainting). Consideration should be given to the following: – Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors. – In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended dose. – In those patients already taking an optimized dose of PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor. – Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

Renal Insufficiency HAVIDOL should be limited to 5 mg not more than once daily in patients with severe renal insufficiency or end-stage renal disease. The starting dose of HAVIDOL in patients with a moderate degree of renal insufficiency should be 5 mg not more than once daily, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. No dose adjustment is required in patients with mild renal insufficiency (see Pharmacokinetics in Special Populations under CLINICAL PHARMACOLOGY).

Hepatic Impairment In patients with mild or moderate hepatic impairment, the dose of HAVIDOL should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of HAVIDOL in this group is not recommended (see Pharmacokinetics in Special Populations under CLINICAL PHARMACOLOGY).

Concomitant Use of Potent Inhibitors of Cytochrome P450 3A4 (CYP3A4) HAVIDOL is metabolized predominantly by CYP3A4 in the liver. The dose of HAVIDOL should be limited to 10 mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, and itraconazole (see Effects of Other Drugs on HAVIDOL under Drug Interactions).

General As with other PDE5 inhibitors, avafynetyne HCl has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, avafynetyne HCl 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mm Hg in healthy subjects (see Pharmacodynamics under CLINICAL PHARMACOLOGY). While this effect should not be of consequence in most patients, prior to prescribing HAVIDOL, physicians should carefully consider

whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with significant left ventricular outflow obstruction or severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators. The safety and efficacy of combinations of HAVIDOL and other treatments for DSACDAD have not been studied. Therefore, the use of such combinations is not recommended. HAVIDOL should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease). When administered in combination with aspirin, avafynetyne HCl 20 mg did not prolong bleeding time, relative to aspirin alone. HAVIDOL has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although HAVIDOL has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

Information for Patients Physicians should discuss with patients the contraindication of HAVIDOL with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of HAVIDOL with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke. Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of HAVIDOL. In such a patient, who has taken HAVIDOL, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of HAVIDOL before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking HAVIDOL should seek immediate medical attention. Physicians should advise patients to stop use of all PDE5 inhibitors, including HAVIDOL, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5

inhibitors (see Postmarketing surveillance, Ophthalmologic under ADVERSE REACTIONS). Physicians should discuss with patients the potential for HAVIDOL to augment the blood-pressure-lowering effect of alpha-blockers and anti-hypertensive medications. Patients should be made aware that both alcohol and HAVIDOL, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with HAVIDOL can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Physicians should consider the potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and seek immediate medical attention. There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention. The use of HAVIDOL offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered. Patients should read the patient leaflet entitled "INFORMATION FOR THE PATIENT" before starting therapy with HAVIDOL and each time the prescription is renewed or refilled.

Drug Interactions Effects of Other Drugs on HAVIDOL Cytochrome P450 Inhibitors HAVIDOL is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase avafynetyne HCl exposure (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Ketoconazole — Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased avafynetyne HCl 20-mg single-dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for avafynetyne HCl 20 mg alone. Ketoconazole (200 mg daily) increased avafynetyne HCl 10-mg single-dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for avafynetyne HCl 10 mg alone. HIV Protease inhibitor — Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased avafynetyne HCl 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in C_{max}, relative to the values for avafynetyne HCl 20 mg alone. Ritonavir (200 mg twice daily), increased avafynetyne HCl 20-mg single-dose exposure (AUC) by 124% with

no change in C_{max}, relative to the values for avafynetyne HCl 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase avafynetyne HCl exposure (see DOSAGE AND ADMINISTRATION). Based upon these results, in patients taking concomitant potent CYP3A4 inhibitors, the dose of HAVIDOL should not exceed 10 mg, and HAVIDOL should not be taken more frequently than once in every 72 hours (see DOSAGE AND ADMINISTRATION). Other cytochrome P450 inhibitors — Although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase avafynetyne HCl exposure. Cytochrome P450 Inducers Studies have shown that drugs that induce CYP3A4 can decrease avafynetyne HCl exposure.

Rifampin —

Rifampin (600 mg daily), a CYP3A4 inducer, reduced avafynetyne HCl 10-mg single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for avafynetyne HCl 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease avafynetyne HCl exposure. No dose adjustment is warranted. Gastrointestinal Drugs H₂ antagonists — An increase in gastric pH resulting from administration of nizatidine had no significant effect on avafynetyne HCl pharmacokinetics. Antacids — Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and avafynetyne HCl reduced the apparent rate of absorption of avafynetyne HCl without altering exposure (AUC) to avafynetyne HCl. Effects of HAVIDOL on Other Drugs Drugs Metabolized by Cytochrome P450 HAVIDOL is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that avafynetyne HCl does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. CYP1A2 substrate — avafynetyne HCl had no clinically significant effect on the pharmacokinetics of theophylline. When avafynetyne HCl was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed. CYP3A4 substrates — avafynetyne HCl had no clinically significant effect on exposure (AUC) to midazolam or lovastatin.

CYP2C9 substrate — avafynetyne HCl had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did avafynetyne HCl affect changes in prothrombin time induced by warfarin. Alcohol Alcohol and PDE5 inhibitors, including avafynetyne HCl, are mild systemic vasodilators. The interaction of avafynetyne HCl with alcohol was evaluated in 3 clinical pharmacology studies. In 2 of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately 6 ounces of 80-proof vodka in an 80-kg subject, and avafynetyne HCl was administered at a dose of 10 mg in 1 study and 20 mg in another. In both these studies, all patients imbibed

the entire alcohol dose within 10 minutes of starting. In one of these two studies, blood alcohol levels of 0.08% were confirmed. In these two studies, more patients had clinically significant decreases in blood pressure on the combination of avafynetyne HCl and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When avafynetyne HCl 20 mg was administered with a lower dose of alcohol (0.6 g/kg, which is equivalent to approximately 4 ounces of 80-proof vodka, administered in less than 10 minutes), orthostatic hypotension was not observed, dizziness occurred with similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated. avafynetyne HCl did not affect alcohol plasma concentrations and alcohol did not affect avafynetyne HCl plasma concentrations. Both alcohol and HAVIDOL, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with HAVIDOL can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Anti-Hypertensives PDE5 inhibitors, including avafynetyne HCl, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of avafynetyne HCl on the potentiation of the blood-pressure-lowering effects of selected anti-hypertensive medications. Alpha Blockers Clinical pharmacology studies were conducted to investigate the potential interaction of avafynetyne HCl with alpha-blocker agents. In these studies, a single oral dose of avafynetyne HCl was administered to healthy subjects taking daily (at least 7 days duration) oral alpha-blocker. The studies were randomized, double-blinded, crossover designs. Tamsulosin — A single oral dose of avafynetyne HCl 10, 20 mg, or placebo was administered in a 3-period, crossover design to healthy subjects taking 0.4 mg once-daily tamsulosin, a selective alpha[1A]-adrenergic blocker (N=18 subjects). avafynetyne HCl or placebo was administered 2 hours after tamsulosin following a minimum of seven days of tamsulosin dosing. Table 7: Tamsulosin Study: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Group	Mean Maximal Decrease (mm Hg)	95% CI
Placebo-subtracted	3.2	(-2.3, 8.6)
avafynetyne HCl 10 mg	3.2	(-2.3, 8.7)
avafynetyne HCl 20 mg	1.7	(-4.7, 8.1)
Supine	2.3	(-4.1, 8.7)

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after avafynetyne HCl or placebo dosing. There were 2, 2, and 1 outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points) following administration of avafynetyne HCl 10 mg, 20 mg, and placebo, respectively. There were no subjects with a standing systolic blood pressure <85 mm Hg. No severe adverse events potentially

related to blood-pressure effects were reported. No syncope was reported.

Doxazosin — Two clinical pharmacology studies were conducted with avafynetyne HCl and doxazosin, an alpha[1]-adrenergic blocker. In the first doxazosin study, a single oral dose of avafynetyne HCl 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking oral doxazosin 8 mg daily (N=18 subjects). Doxazosin was administered at the same time as avafynetyne HCl or placebo after a minimum of seven days of doxazosin dosing. Table 8: Doxazosin Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg) avafynetyne HCl 20 mg Supine 3.6 (-1.5, 8.8) Standing 9.8 (4.1, 15.5) Figure 3: Doxazosin Study 1: Mean Change from Baseline in Systolic Blood Pressure Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after avafynetyne HCl or placebo administration. Outliers were defined as subjects with a standing systolic blood pressure of <85 mm Hg or a decrease from baseline in standing systolic blood pressure of 30 mm Hg at one or more time points. There were 9 and 3 outliers following administration of avafynetyne HCl 20 mg and placebo, respectively. Five and two subjects were outliers due to a decrease from baseline in standing systolic BP of >30 mm Hg, while five and one subject were outliers due to standing systolic BP <85 mm Hg following avafynetyne HCl and placebo, respectively. Severe adverse events potentially related to blood-pressure effects were assessed. No such events were reported following placebo. Two such events were reported following administration of avafynetyne HCl. Vertigo was reported in one subject that began 7 hours after dosing and lasted about 5 days. This subject previously experienced a mild episode of vertigo on doxazosin and placebo. Dizziness was reported in another subject that began 25 minutes after dosing and lasted 1 day. No syncope was reported. In the second doxazosin study, a single oral dose of avafynetyne HCl 20 mg was administered to healthy subjects taking oral doxazosin, either 4 or 8 mg daily. The study (N=72 subjects) was conducted in three parts, each a 3-period crossover. In part A (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 a.m. avafynetyne HCl was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control. In part B (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 p.m. avafynetyne HCl was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control. In part C (N=24), subjects were titrated to doxazosin 8 mg administered daily at 8 a.m. In this part, avafynetyne HCl or placebo were administered at either 8 a.m. or 8 p.m. The placebo-subtracted mean maximal decreases in systolic blood pressure over a 12-hour period after dosing in the placebo-controlled portion of the study (part C) are shown in the following table. Table 9: Doxazosin Study 2 (Part C): Mean Maximal Decrease in Systolic Blood Pressure Placebo-subtracted mean

maximal decrease in systolic blood pressure (mm Hg) avafynetyne HCl 20 mg at 8 a.m. avafynetyne HCl 20 mg at 8 p.m. Ambulatory Blood-Pressure Monitoring (ABPM)

Figure 4: Doxazosin Study 2 (Part C): Mean Change from Time-Matched Baseline in Systolic Blood Pressure Blood pressure was measured by ABPM every 15 to 30 minutes for up to 36 hours after avafynetyne HCl or placebo. Subjects were categorized as outliers if one or more systolic blood pressure readings of <85 mm Hg were recorded or one or more decreases in systolic blood pressure of 30 mm Hg from a time-matched baseline occurred during the analysis interval. Of the 24 subjects in part C, 16 subjects were categorized as outliers following administration of avafynetyne HCl and 6 subjects were categorized as outliers following placebo during the 24-hour period after 8 a.m. dosing of avafynetyne HCl or placebo. Of these, 5 and 2 were outliers due to systolic BP <85 mm Hg, while 15 and 4 were outliers due to a decrease from baseline in systolic BP of 30 mm Hg following avafynetyne HCl and placebo, respectively. During the 24-hour period after 8 p.m. dosing, 17 subjects were categorized as outliers following administration of avafynetyne HCl and 7 subjects following placebo. Of these, 10 and 2 subjects were outliers due to systolic BP <85 mm Hg, while 15 and 5 subjects were outliers due to a decrease from baseline in systolic BP of >30 mm Hg, following avafynetyne HCl and placebo, respectively. Some additional subjects in both the avafynetyne HCl and placebo groups were categorized as outliers in the period beyond 24 hours. Severe adverse events potentially related to blood-pressure effects were assessed. In the study (N=72 subjects), 2 such events were reported following administration of avafynetyne HCl (symptomatic hypotension in one subject that began 10 hours after dosing and lasted approximately 1 hour, and dizziness in another subject that began 11 hours after dosing and lasted 2 minutes). No such events were reported following placebo. In the period prior to avafynetyne HCl dosing, one severe event (dizziness) was reported in a subject during the doxazosin run-in phase. Alfuzosin — A single oral dose of avafynetyne HCl 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking once-daily alfuzosin HCl 10 mg extended-release tablets, an alpha[1]-adrenergic blocker (N=17 completed subjects). avafynetyne HCl or placebo was administered 4 hours after alfuzosin following a minimum of seven days of alfuzosin dosing. Table 10: Alfuzosin Study: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg) avafynetyne HCl 20 mg Supine 2.2 (-0.9, 5.2) Standing 4.4 (-0.2, 8.9) Blood pressure was measured manually at 1, 2, 3, 4, 6, 8, 10, 20, and 24 hours after avafynetyne HCl or placebo dosing. There was 1 outlier (subject with a standing systolic blood pressure <85 mm Hg) following administration of avafynetyne HCl 20 mg. There were no subjects with a decrease from

baseline standing systolic blood pressure of >30 mm Hg at one or more time points. No severe adverse events potentially related to blood pressure effects were reported. No syncope was reported. Other Anti-Hypertensive Agents

Amlodipine

— A study was conducted to assess the interaction of amlodipine (5 mg daily) and avafynetyne HCl 10 mg. There was no effect of avafynetyne HCl on amlodipine blood levels and no effect of amlodipine on avafynetyne HCl blood levels. The mean reduction in supine systolic/diastolic blood pressure due to avafynetyne HCl 10 mg in subjects taking amlodipine was 3/2 mm Hg, compared to placebo. In a similar study using avafynetyne HCl 20 mg, there were no clinically significant differences between avafynetyne HCl and placebo in subjects taking amlodipine. Metoprolol — A study was conducted to assess the interaction of sustained-release metoprolol (25 to 200 mg daily) and avafynetyne HCl 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to avafynetyne HCl 10 mg in subjects taking metoprolol was 5/3 mm Hg, compared to placebo. Bendrofluazide — A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and avafynetyne HCl 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to avafynetyne HCl 10 mg in subjects taking bendrofluazide was 6/4 mm Hg, compared to placebo.

Enalapril

— A study was conducted to assess the interaction of enalapril (10 to 20 mg daily) and avafynetyne HCl 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to avafynetyne HCl 10 mg in subjects taking enalapril was 4/1 mm Hg, compared to placebo.

Angiotensin II receptor blocker (and other anti-hypertensives) — A study was conducted to assess the interaction of angiotensin II receptor blockers and avafynetyne HCl 20 mg. Subjects in the study were taking any marketed angiotensin II receptor blocker, either alone, as a component of a combination product, or as part of a multiple anti-hypertensive regimen. Following dosing, ambulatory measurements of blood pressure revealed differences between avafynetyne HCl and placebo of 8/4 mm Hg in systolic/diastolic blood pressure. Aspirin avafynetyne HCl did not potentiate the increase in bleeding time caused by aspirin.

Carcinogenesis, Mutagenesis, Impairment of Fertility avafynetyne HCl was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 400 mg/kg/day. Systemic drug exposures, as measured by AUC of unbound avafynetyne HCl, were approximately 10-fold for mice, and 14- and 26-fold for male and female rats, respectively, the exposures in human males given Maximum Recommended Human Dose (MRHD) of 20 mg. Avafynetyne HCl was not mutagenic in the in vitro bacterial Ames assays or the forward

mutation test in mouse lymphoma cells. avafynetyne HCl was not clastogenic in the in vitro chromosomal aberration test in human lymphocytes or the in vivo rat micronucleus assays. There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of avafynetyne HCl up to 400 mg/kg/day, a dose producing AUCs for unbound avafynetyne HCl of 14-fold for males or 26-fold for females the exposures observed in human males given the MRHD of 20 mg. In beagle dogs given avafynetyne HCl daily for 3 to 12 months, there was treatment-related non-reversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20-100% of the dogs that resulted in a decrease in spermatogenesis in 40-75% of the dogs at doses of ≥ 10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect-level (NOAEL) (10 mg/kg/day) for unbound avafynetyne HCl was similar to that expected in humans at the MRHD of 20 mg. There were no treatment-related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

Animal Toxicology Animal studies showed vascular inflammation in avafynetyne HCl-treated mice, rats, and dogs. In mice and rats, lymphoid necrosis and hemorrhage were seen in the spleen, thymus, and mesenteric lymph nodes at unbound avafynetyne HCl exposure of 2- to 33-fold above the human exposure (AUCs) at the MRHD of 20 mg. In dogs, an increased incidence of disseminated arteritis was observed in 1- and 6-month studies at unbound avafynetyne HCl exposure of 1- to 54-fold above the human exposure (AUC) at the MRHD of 20 mg. In a 12-month dog study, no disseminated arteritis was observed, but 2 dogs exhibited marked decreases in white blood cells (neutrophils) and moderate decreases in platelets with inflammatory signs at unbound avafynetyne HCl exposures of approximately 14- to 18-fold the human exposure at the MRHD of 20 mg. The abnormal blood-cell findings were reversible within 2 weeks upon removal of the drug.

Pregnancy, Nursing Mothers, and Pediatric Use HAVIDOL is not indicated for use in newborns or children. Avafynetyne HCl and/or its metabolites cross the placenta, resulting in fetal exposure in rats. Avafynetyne HCl and/or its metabolites were secreted into the milk in lactating rats at concentrations approximately 2.4-fold greater than found in the plasma. Following a single-oral dose of 10 mg/kg, approximately 0.1% of the total radioactive dose was excreted into the milk within 3 hours. It is not known if avafynetyne HCl and/or its metabolites is excreted in human breast milk. Use of avafynetyne HCl in nursing mothers is not recommended. Pregnancy Category B — There was no evidence of teratogenicity, embryotoxicity, or fetotoxicity in rat or mouse fetuses that received up to 1000 mg/kg/day during the major organ development. Plasma exposure at this dose is approximately 11-fold greater than the AUC values for unbound avafynetyne

HCl in humans given the MRHD of 20 mg. In a rat prenatal and postnatal development study at doses of 60, 200, and 1000 mg/kg, there was a reduction in postnatal survival of pups. The no-observed-effect-level (NOEL) for maternal toxicity was 200 mg/kg/day and for developmental toxicity was 30 mg/kg/day, which gives approximately 16- and 10-fold exposure multiples, respectively, of the human AUC for the MRHD dose of 20 mg. There are no adequate and well-controlled studies of avafynetyne HCl in pregnant women.

Geriatric Use No overall differences in efficacy and safety were observed between older and younger patients. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered (see Special Populations under CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS Avafynetyne HCl was administered to over 5700 subjects (ranging from 19 to 87 years) during clinical trials worldwide. Over 1000 patients were treated for 1 year or longer and over 1300 patients were treated for 6 months or more. In placebo-controlled Phase 3 clinical trials, the discontinuation rate due to adverse events in patients treated with avafynetyne HCl 20 mg was 3.1%, compared to 1.4% in placebo-treated patients. When avafynetyne HCl was taken as recommended in the placebo-controlled clinical trials, the following adverse events were reported (see Table 11):

Adverse Event	Placebo (N=476)	avafynetyne HCl 5 mg (N=151)	avafynetyne HCl 10 mg (N=394)	avafynetyne HCl 20 mg (N=635)
Headache	5%	11%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal congestion	1%	2%	3%	3%
Flushing*	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

* The term flushing includes: facial flushing and flushing. Back pain or myalgia was reported at incidence rates described in Table 11. In avafynetyne HCl clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with avafynetyne HCl treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbancy. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported infrequently (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required

treatment, a mild narcotic (e.g., codeine) was used. Overall, approximately 0.5% of all avafynetyne HCl-treated subjects discontinued treatment as a consequence of back pain/myalgia. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology. Across all studies with any avafynetyne HCl dose, reports of changes in color vision were rare (<0.1% of patients). The following section identifies additional, less frequent events (<2%) reported in controlled clinical trials; a causal relationship of these events to HAVIDOL is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and reports too imprecise to be meaningful: Body as a whole: asthenia, face edema, fatigue, pain Cardiovascular: angina pectoris, chest pain, hypotension, hypertension, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia Digestive: abnormal liver function tests, diarrhea, dry mouth, dysphagia, esophagitis, gastroesophageal reflux, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting Musculoskeletal: arthralgia, neck pain Nervous: dizziness, hypesthesia, insomnia, paresthesia, somnolence, vertigo Respiratory: dyspnea, epistaxis, pharyngitis Skin and Appendages: pruritus, rash, sweating Ophthalmologic: blurred vision, changes in color vision, conjunctivitis (including conjunctival hyperemia), eye pain, lacrimation increase, swelling of eyelids Urogenital: erection increased, spontaneous penile erection

Postmarketing surveillance Cardiovascular and cerebrovascular: Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of avafynetyne HCl. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of HAVIDOL without sexual activity. Others were reported to have occurred hours to days after the use of HAVIDOL and sexual activity. It is not possible to determine whether these events are related directly to HAVIDOL, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see WARNINGS for additional information). Other adverse events: The following list includes other adverse events that have been identified during postmarketing use of HAVIDOL. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency

or establish a causal relationship to drug exposure.

Body as a whole: hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis

Nervous: migraine

Ophthalmologic: visual field defect, retinal vein occlusion, retinal artery occlusion Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including HAVIDOL. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (see Information for Patients under PRECAUTIONS).

Urogenital: priapism (see WARNINGS)

OVERDOSAGE Single doses up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Hemodialysis contributes negligibly to avafynetyne HCl elimination.

DOSAGE AND ADMINISTRATION The recommended starting dose of HAVIDOL in most patients is 20 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients. HAVIDOL was shown to improve DSACDAD compared to placebo. Therefore, when advising patients on optimal use of HAVIDOL, this should be taken into consideration. HAVIDOL may be taken without regard to food. Renal Insufficiency — No dose adjustment is required in patients with mild renal insufficiency. For patients with moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency, a starting dose of 5 mg not more than once daily is recommended, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. For patients with severe (creatinine clearance <30 mL/min) renal insufficiency on hemodialysis, the maximum recommended dose is 5 mg (see General and Patients with Renal Insufficiency under PRECAUTIONS and Pharmacokinetics in Special Populations under CLINICAL PHARMACOLOGY). Hepatic Impairment — For patients with mild or moderate degrees of hepatic impairment (Child-Pugh Class A or B), the dose of HAVIDOL should not exceed 10 mg once daily. In patients with severe hepatic impairment (Child-Pugh Class C), the use of HAVIDOL is not recommended

(see Patients with Hepatic Impairment under PRECAUTIONS and Pharmacokinetics in Special Populations under CLINICAL PHARMACOLOGY).
Concomitant Medications —

When HAVIDOL is coadministered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating treatment with HAVIDOL, and HAVIDOL should be initiated at the lowest recommended dose (see PRECAUTIONS). For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of HAVIDOL is 10 mg, not to exceed once every 72 hours (see PRECAUTIONS). Concomitant use of nitrates in any form is contraindicated (see CONTRAINDICATIONS).

Geriatrics — No dose adjustment is required in patients >65 years of age.

HOW SUPPLIED HAVIDOL® (avafynetyne HCl) is supplied as follows: One strength of film-coated, circular blue tablets is available 20-mg tablets debossed with "HAVIDOL 247365" Bottles of 30 NDC 0002-4464-30 Store at 25°C (77°F);

excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. One strength of suppository, 20mg.

Keep out of reach of children.

Literature revised February 8, 2007

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