Firstmed Pharma

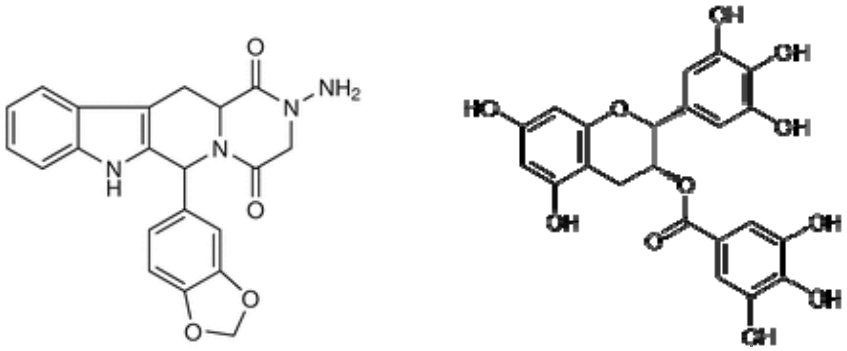
GIOXIL-36

CAPSULES

OTC

DESCRIPTION

GIOXIL-36 is indicated for the treatment of erectile dysfunction. Its composition is formulated from natural products **Maca Root** 200mg (Lepidium meyenii)and **Muira puama** 20mg(Ptychopetalum olacoides) , Hydroxyhomosildenafil 20mg



GIOXIL-36 is beige to brownish powder (80 mesh) with a solubility of 2.5mg/ml in pH 5.2 water. Each GIOXIL-36 capsule contains 240mg of the formulated natural components. Each capsule shell contains gelatin, titanium dioxide and FD&C Blue top white base No. 1.

CLINICAL PHARMACOLOGY

Mechanism of Action

Maca's reported beneficial effects for sexual function could be due to its high concentration of proteins and vital nutrients though Maca contains a chemical called p-methoxybenzyl isothiocyanate, which reputedly has aphrodisiac properties. Maca may contain phyto-estrogens as occurs in other plants. Phyto-estrogens may have estrogenic or anti-estrogenic activities (Kuiper et al. 1998).Recently; remarkable progress has been made in our understanding of the role of sex steroids in human male physiology. A possible role of estrogens in both human male fertility and sexuality has also been suggested by recent studies (Rochira et al. 2001). A well-established effect of estrogens has been provided by recent studies on male rodents, which show impaired sexual behavior and fertility as a consequence of estrogen defect (O'Donnell et al. 2001). The emerging physiological role of estrogens in male fertility suggests that estrogenic substances should be considered 'male hormones' (O'Donnell et al. 2001). At this time it is difficult to conclude that treatment with Maca contributes a male hormone in the form of phytoestrogens which would lead to improvement in sexual function. Further studies will be required to clarify the mechanism of action of Maca on male sexuality and fertility. Maca, when used appropriately, appears to be relatively safe.

Fertility-enhancing properties of maca are thought to be due to aromatic isothiocyanates hydrolyzed from these glucosinolates. Furthermore, benzyl isothiocyanate has been reported to inhibit breast, stomach and liver cancer in rats. Aphrodisiacal properties are attributed to the prostaglandins, sterols and amides of polyunsaturated fatty acids The most confounding question about maca's effect is its ability to influence sexual performance without affecting serum hormone levels such as luteinizing hormone, follicle stimulating hormone, prolactin, testosterone and estradiol It is therefore assumed that maca acts on the receptors for these hormones Both methanolic and acqueous extracts of Maca exhibit estrogenic activity in vitro Alkaloids purified from the maca root are thought to affect the hypothalamic-pituitary axis, explaining why maca can induce effects in both sexes

Muira puama (*Ptychopetalum olacoides*)is a small tree native to the Brazilian Amazon where the stems and roots are used as a tonic for neuromuscular problems. A root decoction is used externally in massages and baths for paralysis and beriberi. Oral use of tea made from the roots for sexual impotence, rheumatism, and GI problems has been noted

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function byincreasing the amount of cGMP. GIOXIL-36 inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by GIOXIL-36 has no effect in the absence of sexual stimulation.

Studies in vitro have demonstrated that GIOXIL-36 is a selective inhibitor of PDE5. PDE5 is found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas. In vitro studies have shown that the effect of GIOXIL-36 is more potent on PDE5 than on other phosphodiesterases. These studies have shown that GIOXIL-36 is >8,000-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. GIOXIL-36 is >8,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, GIOXIL-36 is 600-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. GIOXIL-36 is >7,000-fold more potent for PDE5 than for 10 PDE8, PDE9, and PDE10. GIOXIL-36 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, GIOXIL-36 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

Absorption

GIOXIL-36 well absorbed from an oral dose, with about 70 percent ending up in the bloodstream. After single oral-dose administration, the maximum observed plasma concentration (Cmax) of GIOXIL-36 is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of GIOXIL-36 l following oral dosing has not been determined. The rate and extent of absorption of GIOXIL-36 are not influenced by food; thus GIOXIL-36 may be taken with or without food.

Distribution

The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that GIOXIL-36 l is distributed into tissues. At therapeutic concentrations, 94% of GIOXIL-36 l in plasma is bound to proteins. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism

GIOXIL-36 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

Following a single dose of 240mg GIOXIL-36 in normal weight and obese subjects, fecal and urine excretion of the unabsorbed product was found to be the major route of elimination. The mean oral clearance for GIOXIL-36 is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. GIOXIL-36 l 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).

Special Populations

Geriatrics: Plasma concentrations of Maca and Muira puama were similar between elderly (ages 61 to 75yr) and younger (ages 17-30) subjects following a single dose of 240mg oral GIOXIL-36 . In general, dose selection for the elderly should be cautious, reflecting the greater frequency for decreased hepatic, renal, or other product therapy.

Pediatrics: GIOXIL-36 has not been evaluated in individuals less than 18 years old.

Patients with Diabetes Mellitus: In male patients with diabetes mellitus after a 240 mg GIOXIL-36 dose, exposure (AUC) was reduced approximately 19% and Cmax was 5% lower than that observed in healthy subjects. No dose adjustment is warranted

DRUG-DRUG INTERACTIONS

Drug-drug interaction studies indicate that GIOXIL-36 had no effect on pharmacokinetics and /or pharmacodynamics of alcohol, digoxin, gylburide, nifedipine, oral contraceptives, phenytoin, pravastatin. Alcohol did not affect the pharmacodynamics of GIOXIL-36.

Effects on Blood Pressure When Administered with Nitrates

In clinical pharmacology studies, GIOXIL-36 (100 to 240 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of GIOXIL-36 in patients taking any form of nitrates is contraindicated [see Contraindications].

A study was conducted to assess the degree of interaction between nitroglycerin and GIOXIL-36, should nitroglycerin be required in an emergency situation after GIOXIL-36 was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of GIOXIL-36 240 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 GIOXIL-36 (2, 4, 8, 24, 48, 72, and 96 hours after GIOXIL-36). The objective of the study was to determine when, after GIOXIL-36 dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between GIOXIL-36 and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between GIOXIL-36 and NTG was not observed, although a few more GIOXIL-36 subjects compared to placebo experienced greater blood-pressure lowering at this timepoint. After 48 hours, the interaction was not detectable (see Figure 1).

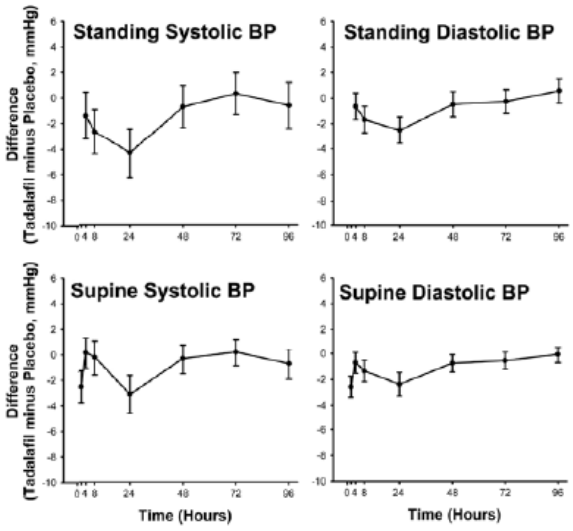


Figure 1: Mean Maximal Change in Blood Pressure (GIOXIL-36 Minus Placebo, Point Estimate with 90% CI) in Response to Sublingual Nitroglycerin at 2 (Supine Only), 4, 8, 24, 48, 72, and 96 Hours after the Last Dose of GIOXIL-36 240 mg or Placebo.

Therefore, GIOXIL-36 administration with nitrates is contraindicated. In a patient who has taken GIOXIL-36, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of GIOXIL-36 before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring [see Contraindications].

Effect on Blood Pressure When Administered With Alpha Blockers

Six randomized, double-blinded, crossover clinical pharmacology studies were conducted to investigate the potential interaction of GIOXIL-36 with alpha-blocker agents in healthy male subjects [see Dosage and Administration (2.4) and Warnings and Precautions (5.6)]. In four studies, a single oral dose of GIOXIL-36 was administered to healthy male subjects taking daily (at least 7 days duration) oral alpha blocker. In two studies, daily oral alpha blocker (at least 7 days duration) was administered to healthy male subjects taking repeated daily doses of GIOXIL-36.

Doxazosin — Three clinical pharmacology studies were conducted with GIOXIL-36 and doxazosin, an alpha[1]-adrenergic blocker. In the first doxazosin study, a single oral dose of GIOXIL-36 240 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 GIOXIL-36 or placebo after a minimum of seven days of doxazosin dosing.

Effects on Blood Pressure When Administered with Antihypertensives

Amlodipine — A study was conducted to assess the interaction of amlodipine (5 mg daily) and GIOXIL-36 200 mg. There was no effect of GIOXIL-36 on amlodipine blood levels and no effect of amlodipine on GIOXIL-36 blood levels. The mean reduction in supine systolic/diastolic blood pressure due to GIOXIL-36 200 mg in subjects taking amlodipine was 3/2 mm Hg, compared to placebo. In a similar study using GIOXIL-36 240 mg, there were no clinically significant differences between GIOXIL-36 and placebo in subjects taking amlodipine.

Angiotensin II receptor blockers (with and without other antihypertensives) — A study was conducted to assess the interaction of angiotensin II receptor blockers and GIOXIL-36 240 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 antihypertensive regimen. Following dosing, ambulatory measurements of blood pressure revealed differences between GIOXIL-36 and placebo of 8/4 mm Hg in systolic/diastolic blood pressure.

Bendrofluazide — A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and GIOXIL-36 200 mg.

Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to GIOXIL-36 240mg in subjects taking bendrofluazide was 6/4 mm Hg, compared to placebo.

Enalapril — A study was conducted to assess the interaction of enalapril (100 to2000 mg daily) and GIOXIL-36 240 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to GIOXIL-36 200 mg in subjects taking enalapril was 4/1 mm Hg, compared to placebo.

Metoprolol — A study was conducted to assess the interaction of sustained-release metoprolol (25 to 200 mg daily) and GIOXIL-36 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to GIOXIL-36 200 mg in subjects taking metoprolol was 5/3 mm Hg, compared to placebo.

Effects on Blood Pressure When Administered with Alcohol

Alcohol and PDE5 inhibitors, including GIOXIL-36, are mild systemic vasodilators. The interaction of GIOXIL-36 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 male, and GIOXIL-36 was administered at a dose of 200 mg in one study and 240 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 GIOXIL-36 and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When GIOXIL-36 240 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.

GIOXIL-36 did not affect alcohol plasma concentrations and alcohol did not affect GIOXIL-36 plasma concentrations.

CLINICAL STUDIES

The efficacy and safety of GIOXIL-36 in the treatment of erectile dysfunction has been evaluated in 22 clinical trials of up to 24-weeks duration, involving over 4000 patients. GIOXIL-36 , when taken as needed up to once per day, was shown to be effective in improving erectile function in men with erectile dysfunction (ED). GIOXIL-36 was studied in the general ED 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 3 were conducted in centers outside the US. Additional efficacy and safety studies were performed in ED patients with diabetes mellitus and in patients who developed ED status post bilateral nerve-sparing radical prostatectomy.

In these 5 trials, GIOXIL-36 was taken as needed, at doses ranging from 100 to 240 mg, up to once per day. 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 GIOXIL-36 on erectile function. The 3 primary outcome measures were the Erectile Function (EF) domain of the International Index of Erectile Function (IIEF) and Questions 2 and 3 from Sexual Encounter Profile (SEP). The IIEF 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 IIEF EF 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 insert your penis into the partner’s vagina?” SEP Question 3 asks, “Did your erection last long enough for you to have successful

intercourse?" The overall percentage of successful attempts to insert the penis into the vagina (SEP2) and to maintain the erection for successful intercourse (SEP3) is derived for each patient.

Results in ED Population in US Trials — The 2 primary US efficacy and safety trials included White, 14% Black, 7% Hispanic, and 1% of other ethnicities, and included patients with ED 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 ED 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, GIOXIL-36 240 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables *(see Table 1)*. The treatment effect of GIOXIL-36 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	**GIOXIL-36 240mg**	**p-value**	**Placebo**	**GIOXIL-36 240mg**	**p-value**
	N=62	N=281		N=73	N=168	
EF Domain Score						
Endpoint	14.7	19.8		13.6	22.5	
Change from baseline	-0.4	7.2	<.001	3	9.4	<.001
Insertion of Penis						
Endpoint	36%	61%		40%	74%	
Change from baseline	2%	25%	<.001	2%	33%	<.001
Maintenance of Erection (SEP3)						
Endpoint	27%	52%		22%	63%	
Change from baseline	5%	35%	<.001	4%	46%	<.001

Results in General ED Population in Trials Outside the US — The 3 primary efficacy and safety studies conducted in the general ED 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 ED 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 ED of at least 1-year duration. In these 5 trials, GIOXIL-36 200 and 240 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (see Tables 2, 3 and 4). The treatment effect of GIOXIL-36 did not diminish over time.

Table 2: Mean Endpoint and Change from Baseline for the EF Domain of the IIEF in the General ED Population in Three Primary Trials Outside the US

Trial Outside United States	**Placebo**	**GIOXIL-36 200mg**	**GIOXIL-36 240mg**
Sudy VC-INT			
Endpoint (Change from baseline)	15.0	18.4	
Study VD-INT			
Endpoint (Change from baseline)	14.3		24.6
Study VE-INT			
Endpoint (Change from baseline)	14.5		26.8

Table 3: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 2 ("Were you able to insert your penis into the partner's vagina?") in the General ED Population in Three Pivotal Trials Outside the US

Trial Outside United States	**Placebo**	**GIOXIL-36 200mg**	**GIOXIL-36 240mg**
Sudy VC-INT			
Endpoint (Change from baseline)	49.2	71.0	
Sudy VD-INT			
Endpoint (Change from baseline)	48.6		85.6
Sudy VE-INT			
Endpoint (Change from baseline)	44.5		87.0

Table 4: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 3 ("Did your erection last long enough for you to have successful intercourse?") in the General ED Population in Three Pivotal Trials Outside the US

Trial Outside United States	**Placebo**	**GIOXIL-36 200mg**	**GIOXIL-36 240mg**
Sudy VC-INT			
Endpoint (Change from baseline)	28	52.0	
Sudy VD-INT			
Endpoint (Change from baseline)	32.7		77.4
Sudy VE-INT			
Endpoint (Change from baseline)	32.3		82.3

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 ED of all degrees of disease severity while taking GIOXIL-36, compared to patients on placebo.

Therefore, in all 7 primary efficacy and safety studies, GIOXIL-36 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 Results in ED Patients with Diabetes Mellitus (DB2)— GIOXIL-36 was shown to be effective in treating ED in patients with diabetes mellitus. Patients with diabetes were included in all 5 primary efficacy studies in the general ED population (N=235) and in one study that specifically assessed GIOXIL-36 in ED patients with type 1 or type 2 diabetes (N=216). In this randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial, GIOXIL-36 demonstrated clinically meaningful and statistically significant improvement in erectile

Table 5: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in ED Patients with Diabetes

Study in subclass DB2	**Placebo**	**GIOXIL-36 200mg**	**GIOXIL-36 240mg**	**p-value**
	N=48	N=63	N=72	
EF Domain Score				
Endpoint (change from baseline)	12.1	19.8	17.6	<.001

Insertion of Penis				
Endpoint (change from baseline)	29%	61%	64%	<.001
Maintenance of Erection (SEP3)				
Endpoint (change from baseline)	20%	52%	52%	<.001

INDICATIONS AND USAGE

GIOXIL-36 is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS

Hypersensitivity to active components. Nitrates , Administration of GIOXIL-36 to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, GIOXIL-36 was shown to potentiate the hypotensive effect of nitrates. This is thought to result from the combined effects of nitrates and GIOXIL-36 on the nitric oxide/cGMP pathway [see Pharmacology].

WARNINGS

No warnings are currently listed for GIOXIL-36 ® due to the botanical nature of the principal ingredients used in the formulation. Evaluation of erectile dysfunction should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options. Before prescribing GIOXIL-36, it is important to note the following:

Cardiovascular

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 GIOXIL-36, should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and seek immediate medical attention. Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of GIOXIL-36. In such a patient, who has taken GIOXIL-36, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of GIOXIL-36 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 GIOXIL-36 should seek immediate medical attention. *[See Contraindications]*.

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. The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for GIOXIL-36, and therefore until further information is available, GIOXIL-36 is not recommended for the following groups of patients:

• myocardial infarction within the last 90 days

• unstable angina or angina occurring during sexual intercourse

• New York Heart Association Class 2 or greater heart failure in the last 6 months

• uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension (>170/100 mm Hg)

• stroke within the last 6 months.

As with other PDE5 inhibitors, GIOXIL-36 has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, GIOXIL-36 240 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 Clinical Pharmacology (12.2)]*. While this effect should not be of consequence in most patients, prior to prescribing GIOXIL-36, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

Prolonged Erection

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.

GIOXIL-36 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).

Eye

Physicians should advise patients to stop use of all PDE5 inhibitors, including GIOXIL-36, 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 Adverse Reactions].

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.

Alpha blockers and Antihypertensives

Physicians should discuss with patients the potential for GIOXIL-36 to augment the blood-pressure-lowering effect of alpha blockers and antihypertensive medications [see Drug

Interactions] and Clinical Pharmacology]. Caution is advised when PDE5 inhibitors are coadministered with alpha blockers. PDE5 inhibitors, including GIOXIL-36, 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 Pharmacology) and Drug Interactions], 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 antihypertensive drugs.

Counseling Patients About Sexually Transmitted Diseases

The use of GIOXIL-36 offers no protection against sexually transmitted diseases. Counseling patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

PRECAUTIONS

Alcohol

Patients should be made aware that both alcohol and GIOXIL-36, 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 GIOXIL-36 can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache

Combination With Other Erectile Dysfunction Therapies

The safety and efficacy of combinations of GIOXIL-36 and other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

MISUSE POTENTIAL

Reports of recreational use and misuse of similar products for erectile dysfunction appear in the medical literature and the media. Increasing access to these products via the Internet may facilitate such misuse. Use in social settings has gained popularity, both in young, healthy patients,

as well as those with chronic medical conditions, including human immunodeficiency virus infections. In these settings, the PDE5 inhibitors are sometimes used concomitantly with "club drugs" such as ketamine and amyl nitrite, leading to potentially harmful or fatal drug interactions. Pharmacists should be cognizant of the potential for PDE5 inhibitors to be misused, particularly in patients who are at greater risk of cardiovascular complications, and should advise patients and other health care professionals accordingly.

USE IN SPECIAL POPULATIONS

Pregnancy

No adequate and well controlled studies with GIOXIL-36 have been conducted in pregnant women. Because animal reproductive studies are not always predicative of human response GIOXIL-36 during pregnancy is not recommended. GIOXIL-36 IS INTENTED FOR MALE USE ONLY.

Nursing Mothers

It is not known if GIOXIL-36 is secretes in human milk. Therefore, GIOXIL-36 should not be taken by nursing women. GIOXIL-36 IS INTENTED FOR MALE USE ONLY.

Pediatric Use

GIOXIL-36 has not been studied in pediatric patients below the age of 12 years.

Geriatric Use

Clinical studies of GIOXIL-36 did not include significant number of patients aged 65 years and older to determine whether the respond differently from younger patients.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. GIOXIL-36 was administered to over 6550 men during clinical trials worldwide. In trials of GIOXIL-36 for once daily use, a total of 716, 389, and 115 were treated for at least 6 months, 1 year, and 2 years, respectively. For GIOXIL-36 for use as needed, over 1300 and 1000 subjects were treated for at least 6 months and 1 year, respectively.

GIOXIL-36 In five primary placebo-controlled Phase 3 studies of 12 weeks duration, mean age was 59 years (range 22 to 88) and the discontinuation rate due to adverse events in patients treated with GIOXIL-36 100 or 240 mg was 3.1%, compared to 1.4% in placebo treated patients.

When taken as recommended in the placebo-controlled clinical trials, the following adverse events were reported (see Table 6) for GIOXIL-36 for use as needed:

Table 6: Treatment-Emergent Adverse Events Reported by ≥2% of Patients Treated with GIOXIL-36 (200 or 240 mg) and More Frequent on Drug than Placebo in the five Primary Placebo-Controlled Phase 3 Studies (Including a Study in Patients with Diabetes) for GIOXIL-36 for Use as Needed

Adverse Event	Placebo (N=320)	GIOXIL-36 100 mg (N=120)	GIOXIL-36 200 mg (N=218)	GIOXIL-36 240 mg (N=472)
Headache	5%	6%	8%	8%
Dyspesia	1%	3%	4%	5%
Back Pain	3%	3%	3%	4%
Nasal Congestion	1%	1%	4%	2%
Facial Flushing	2%	2%	1%	2%
Pain in Limb	1%	1%	3%	3%

Back pain or myalgia was reported at incidence rates described in Table 1. In GIOXIL-36 clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 32 hours. The back pain/myalgia associated with GIOXIL-36 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 with a low frequency (<3% 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 subjects treated with GIOXIL-36 for on demand use discontinued treatment as a consequence of back pain/myalgia. In the 1-year open label extension study, back pain and myalgia were reported in 3%. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology. Across all studies with any GIOXIL-36 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 of GIOXIL-36. A causal relationship of these events to GIOXIL-36 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, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia

Digestive — abnormal liver function tests, dry mouth, dysphagia, esophagitis, 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

Otologic — sudden decrease or loss of hearing, tinnitus

Urogenital — erection increased, spontaneous penile erection

OVERDOSAGE

Single doses up to 2500 mg have been given to healthy subjects, and multiple daily doses up to 800 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 GIOXIL-36 elimination.

DOSAGE AND ADMINISTRATION

Erectile Dysfunction

GIOXIL-36 The recommended starting dose of GIOXIL-36 for use as needed in most patients is 240 mg, taken prior to anticipated sexual activity. The dose may be decreased to 200 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.

GIOXIL-36 for use as needed was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of GIOXIL-36, this should be taken into consideration.

Use with Food

GIOXIL-36 may be taken without regard to food. The safety and effectiveness of GIOXIL-36 beyond 4 years have not been determined at this time.

USE IN SPECIAL POPULATIONS

Geriatrics

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

Hepatic Impairment

GIOXIL-36 Mild or moderate (Child Pugh Class A or B): The dose of GIOXIL-36 should not exceed 200 mg once per day.

HOW SUPPLIED

GIOXIL-36 is a dark –blue hard-gelatin capsule containing powder.
GIOXIL-36 240 mg capsules: Dark –blue two piece No. 0 opaque hard –gelatin capsule. – Box containing 4 capsules in blister cards. Each blister card contains 2 capsules.

Storage Conditions

Store at 25°C (77°F) excursions permitted to 15° to 30°C (59° to 86°F) Keep bottle tightly closed.

GIOXIL-36 should not be used after the given expiration date stamped on the top of the lid of each bottle.

Distributed by:

Firstmed Pharma

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325352

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