SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

PLS NAYGRA 100
(Sildenafil Citrate Tablets 100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each film coated tablet contains:

Sildenafil Citrate Equivalent to Sildenafil 100 mg

Colour: Brilliant blue FCF, Titanium dioxide BP

Excipients: q.s.

S.N.	Ingredients	Spec.	Qty/ Tab (mg)	Ovg. %	Function
1	Sildenafil Citrate Equivalent to Sildenafil	IHS	143.2 ≡ 100	--	Active
2	Micro crystalline cellulose	BP	249.40	--	Diluent
3	Dicalcium phosphate	BP	117.80	--	Diluent
4	Povidone	BP	16.00	--	Binder
5	Isopropyl alcohol	BP	250.00	--	Solvent
	Lubricant				
6	Magnesium stearate	BP	10.00	--	Lubricant
7	Purified talc	BP	9.00	--	Glidant
8	Colloidal anhydrous silica	BP	4.600	--	Lubricant
9	Croscarmellose sodium	BP	22.00	--	Superdisintegrant
10	Micro crystalline cellulose (additional)	BP	10.00	--	Diluent
	Total		**572.00**		
11	Ready coat-blue (brilliant blue FCF)	INH	12.00	--	Colour
12	Purified water	BP	q.s.	--	Solvent
	Total		**584.00**		

Note: Includes additional Microcrystalline cellulose to compensate the loss on drying.

Average weight of uncoated tablet: 572.00 mg ± 5.0%

Average weight of film coated tablet: 584.00 mg ± 5.0%

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

BP: British Pharmacopoeia

INH- IN- House Specification

3. PHARMACEUTICAL FORM

Film coated tablet

4.CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PLS NAYGRA 100 is indicated for the treatment of erectile dysfunction.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Dosage Information

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, PLS NAYGRA 100 may be taken anywhere from 30 minutes to 4 hours before sexual activity. The maximum recommended dosing frequency is once per day.

Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg.

Use with Food

PLS NAYGRA 100 may be taken with or without food.

Dosage Adjustments in Specific Situations

PLS NAYGRA 100 was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors such as organic nitrates or organic nitrites in any form is therefore contraindicated.

When PLS NAYGRA 100 is co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating PLS NAYGRA 100 treatment and PLS NAYGRA 100 should be initiated at 25 mg.

Dosage Adjustments Due to Drug Interactions

Ritonavir

The recommended dose for ritonavir-treated patients is 25 mg prior to sexual activity and the recommended maximum dose is 25 mg within a 48 hours period because concomitant administration increased the blood levels of sildenafil by 11-fold.

CYP3A4 Inhibitors

Consider a starting dose of 25 mg in patients treated with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or saquinavir) or erythromycin. Clinical data have shown that co-administration with saquinavir or erythromycin increased plasma levels of sildenafil by about 3 fold.

2.5 Dosage Adjustments in Special Populations

Consider a starting dose of 25 mg in patients > 65 years, patients with hepatic impairment (e.g., cirrhosis), and patients with severe renal impairment (creatinine clearance <30 mL/minute) because administration of PLS NAYGRA 100 in these patients resulted in higher plasma levels of sildenafil.

4.3 CONTRAINDICATIONS

4.1 Nitrates

Consistent with its known effects on the nitric oxide/cGMP pathway, PLS NAYGRA 100 was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using nitric oxide donors such as organic nitrates or organic nitrites in any form either regularly and/or intermittently is therefore contraindicated.

After patients have taken PLS NAYGRA 100, it is unknown when nitrates, if necessary, can be safely administered. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely co-administered at this time point.

4.2 Hypersensitivity Reactions

PLS NAYGRA 100 is contraindicated in patients with a known hypersensitivity to sildenafil, as contained in PLS NAYGRA 100 or any component of the tablet. Hypersensitivity reactions have been reported, including rash and urticaria.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

5.1 Cardiovascular

There is a potential for cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for erectile dysfunction, including PLS NAYGRA 100, should not be generally used in men for whom sexual activity is inadvisable

because of their underlying cardiovascular status. The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

PLS NAYGRA 100 has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mmHg), While this normally would be expected to be of little consequence in most patients, prior to prescribing PLS NAYGRA 100, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

Use with caution in patients with the following underlying conditions which can be particularly sensitive to the actions of vasodilators including PLS NAYGRA 100 – those with left ventricular outflow obstruction (e.g., aortic stenosis, idiopathic hypertrophic subaortic sten. There are no controlled clinical data on the safety or efficacy of PLS NAYGRA 100 in the following groups; if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;

- Patients with resting hypotension (BP <90/50 mmHg) or hypertension (BP >170/110 mmHg);

- Patients with cardiac failure or coronary artery disease causing unstable angina.

5.2 Prolonged Erection and Priapism

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of PLS NAYGRA 100. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

PLS NAYGRA 100 should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia). However, there are no controlled clinical data on the safety or efficacy of PLS NAYGRA 100 in patients with sickle cell or related anemias.

5.3 Effects on the Eye

Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including PLS NAYGRA 100, 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 rare condition and a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥ 50. An observational study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an

approximate 2 fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. From this information, it is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

Physicians should consider whether their patients with underlying NAION risk factors could be adversely affected by use of PDE5 inhibitors. Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, PDE5 inhibitors, including PLS NAYGRA 100, should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with "crowded" optic disc are also considered at greater risk for NAION compared to the general population, however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including PLS NAYGRA 100, for this uncommon condition.

There are no controlled clinical data on the safety or efficacy of PLS NAYGRA 100 in patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

5.4 Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including PLS NAYGRA 100, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including osis) and those with severely impaired autoPLS NAYGRA 100. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

5.5 Hypotension when Co-administered with Alpha-blockers or Anti-hypertensives

<u>Alpha-blockers</u>

Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including PLS NAYGRA 100, 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 occur. In some patients, concomitant use of these two drug classes can lower blood pressure significantly.

Consideration should be given to the following:

- Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors. Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose.
- In those patients already taking an optimized dose of a 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.

Anti-hypertensives

PLS NAYGRA 100 has systemic vasodilatory properties and may further lower blood pressure in patients taking anti-hypertensive medications.

In a separate drug interaction study, when amlodipine, 5 mg or 10 mg, and PLS NAYGRA 100, 100 mg were orally administered concomitantly to hypertensive patients mean additional blood pressure reduction of 8 mmHg systolic and 7 mmHg diastolic were noted.

5.6 Adverse Reactions with the Concomitant Use of Ritonavir

The concomitant administration of the protease inhibitor ritonavir substantially increases serum concentrations of sildenafil (11-fold increase in AUC). If PLS NAYGRA 100 is prescribed to patients taking ritonavir, caution should be used. Data from subjects exposed to high systemic levels of sildenafil are limited. Decreased blood pressure, syncope, and prolonged erection were reported in some healthy volunteers exposed to high doses of sildenafil (200-800 mg). To decrease the chance of adverse reactions in patients taking ritonavir, a decrease in sildenafil dosage is recommended.

5.7 Combination with other PDE5 Inhibitors or Other Erectile Dysfunction Therapies

The safety and efficacy of combinations of PLS NAYGRA 100 with other PDE5 Inhibitors, including REVATIO or other pulmonary arterial hypertension (PAH) treatments containing sildenafil, or other treatments for erectile dysfunction have not been studied. Such combinations may further lower blood pressure. Therefore, the use of such combinations is not recommended.

5.8 Effects on Bleeding

There have been post-marketing reports of bleeding events in patients who have taken PLS NAYGRA 100. A causal relationship between PLS NAYGRA 100 and these events has not been established. In humans, PLS NAYGRA 100 has no effect on bleeding time when taken alone or with aspirin. However, *in vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). In addition, the combination of heparin and PLS NAYGRA 100 had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

The safety of PLS NAYGRA 100 is unknown in patients with bleeding disorders and patients with active peptic ulceration.

5.9 Counselling Patients About Sexually Transmitted Diseases

The use of PLS NAYGRA 100 offers no protection against sexually transmitted diseases. Counselling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND PHARMACEUTICAL FORM

7.1 Nitrates
Administration of PLS NAYGRA 100 with nitric oxide donors such as organic nitrates or organic nitrites in any form is contraindicated. Consistent with its known effects on the nitric oxide/cGMP pathway, PLS NAYGRA 100 was shown to potentiate the hypotensive effects of nitrates.

7.2 Alpha-blockers
Use caution when co-administering alpha-blockers with PLS NAYGRA 100 because of potential additive blood pressure-lowering effects. When PLS NAYGRA 100 is co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating PLS NAYGRA 100 treatment and PLS NAYGRA 100 should be initiated at the lowest dose.

7.3 Amlodipine
When PLS NAYGRA 100 100 mg was co-administered with amlodipine (5 mg or 10 mg) to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

7.4 Ritonavir and other CYP3A4 inhibitors
Co-administration of ritonavir, a strong CYP3A4 inhibitor, greatly increased the systemic exposure of sildenafil (11-fold increase in AUC). It is therefore recommended not to exceed a maximum single dose of 25 mg of PLS NAYGRA 100 in a 48 hour period.

Co-administration of erythromycin, a moderate CYP3A4 inhibitor, resulted in a 160% and 182% increases in sildenafil C_{max} and AUC, respectively. Co-administration of saquinavir, a strong CYP3A4 inhibitor, resulted in 140% and 210% increases in sildenafil C_{max} and AUC, respectively. Stronger CYP3A4 inhibitors such as ketoconazole or itraconazole could be expected to have greater effects than seen with saquinavir. A starting dose of 25 mg of PLS NAYGRA 100 should be considered in patients taking erythromycin or strong CYP3A4 inhibitors (such as saquinavir, ketoconazole, itracanozole).

7.5 Alcohol
In a drug-drug interaction study sildenafil 50 mg given with alcohol 0.5 g/kg in which mean maximum blood alcohol levels of 0.08% was achieved, sildenafil did not potentiate the hypotensive effect of alcohol in healthy volunteers.

8.1 Pregnancy

Pregnancy Category B. PLS NAYGRA 100 is not indicated for use in women. There are no adequate and well-controlled studies of sildenafil in pregnant women.

Risk Summary Based on animal data, PLS NAYGRA 100 is not predicted to increase the risk of adverse developmental outcomes in humans.

Animal Data No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the Maximum Recommended Human Dose (MRHD) on a mg/m^2 basis in a 50 kg subject. In the rat pre-and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC.

8.4 Paediatric Use

PLS NAYGRA 100 is not indicated for use in paediatric patients. Safety and effectiveness have not been established in paediatric patients.

8.5 Geriatric Use

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil resulting in approximately 84% and 107% higher plasma AUC values of sildenafil and its active N-desmethyl metabolite, respectively, compared to those seen in healthy young volunteers (18-45 years) [*see Clinical Pharmacology (12.3)*]. Due to age-differences in plasma protein binding, the corresponding increase in the AUC of free (unbound) sildenafil and its active N-desmethyl metabolite were 45% and 57%, respectively.

Of the total number of subjects in clinical studies of PLS NAYGRA 100, 18% were 65 years and older, while 2% were 75 years and older. No overall differences in safety or efficacy were observed between older ($\geq$ 65 years of age) and younger (< 65 years of age) subjects.

However, since higher plasma levels may increase the incidence of adverse reactions, a starting dose of 25 mg should be considered in older subjects due to the higher systemic exposure.

8.6 Renal Impairment

No dose adjustment is required for mild (CLcr=50-80 mL/min) and moderate (CLcr=30-49 mL/min) renal impairment. In volunteers with severe renal impairment (Clcr<30 mL/min), sildenafil clearance was reduced, resulting in higher plasma exposure of sildenafil (~2 fold), approximately doubling of C_{max} and AUC. A starting dose of 25 mg should be considered in patients with severe renal impairment.

8.7 Hepatic Impairment
In volunteers with hepatic impairment (Child-Pugh Class A and B), sildenafil clearance was reduced, resulting in higher plasma exposure of sildenafil (47% for C_{max} and 85% for AUC). The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child-Pugh Class C) have not been studied. A starting dose of 25 mg should be considered in patients with any degree of hepatic impairment.

4.6 PREGNANCY AND LACTATION

Pregnancy Category B. PLS NAYGRA 100 is not indicated for use in women. There are no adequate and well-controlled studies of sildenafil in pregnant women.

Risk Summary Based on animal data, PLS NAYGRA 100 is not predicted to increase the risk of adverse developmental outcomes in humans.

Animal Data No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the Maximum Recommended Human Dose (MRHD) on a mg/m^2 basis in a 50 kg subject. In the rat pre-and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC.

Breast Feeding: PLS NAYGRA 100 is not indicated for used in lactating women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Sildenafil tablets can cause dizziness and can affect vision.

4.8 UNDESIRABLE EFFECTS

The following are discussed in more detail in other sections of the labeling:

- Cardiovascular
- Prolonged Erection and Priapism
- Effects on the Eye
- Hearing Loss
- Hypotension when Co-administered with Alpha-blockers or Anti-hypertensives
- Adverse Reactions with the Concomitant Use of Ritonavir
- Combination with other PDE5 Inhibitors or Other Erectile Dysfunction Therapies
- Effects on Bleeding
- Counselling Patients About Sexually Transmitted Diseases

The most common adverse reactions reported in clinical trials ($\geq$ 2%) are headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness, and rash.

In fixed-dose studies, the incidence of some adverse reactions increased with dose. The type of adverse reactions in flexible-dose studies, which reflect the recommended dosage regimen, was

similar to that for fixed-dose studies. At doses above the recommended dose range, adverse reactions were similar to those detailed in Table 1 below but generally were reported more frequently.

Table 1: Adverse Reactions Reported by ≥2% of Patients Treated with PLS NAYGRA 100 and More Frequent than Placebo in Fixed-Dose Phase II/III Studies Adverse Reaction	25 mg (n=312)	50 mg (n=511)	100 mg (n=506)	Placebo (n=607)
Headache	16%	21%	28%	7%
Flushing	10%	19%	18%	2%
Dyspepsia	3%	9%	17%	2%
Abnormal vision†	1%	2%	11%	1%
Nasal congestion	4%	4%	9%	2%
Back pain	3%	4%	4%	2%
Myalgia	2%	2%	4%	1%
Nausea	2%	3%	3%	1%
Dizziness	3%	4%	3%	2%
Rash	1%	2%	3%	1%

Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

Digestive: vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

Hemic and Lymphatic: anemia and leukopenia.

Metabolic and Nutritional: thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.

Respiratory: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and Appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special Senses: sudden decrease or loss of hearing, mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, ear pain, eye hemorrhage, cataract, dry eyes.

Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

Analysis of the safety database from controlled clinical trials showed no apparent difference in adverse reactions in patients taking PLS NAYGRA 100 with and without anti-hypertensive medication. This analysis was performed retrospectively and was not powered to detect any pre-specified difference in adverse reactions.

4.9 OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse reactions were similar to those seen at lower doses but incidence rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS PROPERTIES

Pharmacotherapeutic Category: phosphodiesterase (PDE) inhibitors.
ATC code: G04BE03

PLS NAYGRA 100 (sildenafil citrate), an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

12.1 Mechanism of Action

The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation.

Effects of Sildenafil on Erectile Response: In eight double-blind, placebo-controlled crossover studies of patients with either organic or psychogenic erectile dysfunction, sexual stimulation resulted in improved erections, as assessed by an objective measurement of hardness and duration of erections, after Sildenafil administration compared with placebo. Most studies assessed the efficacy of Sildenafil approximately 60 minutes post dose. The erectile response, as assessed by, generally increased with increasing sildenafil dose and plasma concentration. The time course of effect was examined in one study, showing an effect for up to 4 hours but the response was diminished compared to 2 hours.

Effects of Sildenafil on Blood Pressure: Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in sitting blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8.3/5.3 mmHg). The decrease in sitting blood pressure was most notable approximately 1-2 hours after dosing and was not different than placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg of Sildenafil, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates.

5.2 PHARMACOKINETIC PROPERTIES

Sildenafil is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (range 25-63%). The pharmacokinetics of sildenafil are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly CYP3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil. Both sildenafil and the metabolite have terminal half-lives of about 4 hours.

Absorption and Distribution: Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When Sildenafil is taken with a high fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.
Based upon measurements of sildenafil in semen of healthy volunteers 90 minutes after dosing, less than 0.001% of the administered dose may appear in the semen of patients.

Metabolism and Excretion: Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil and is itself further metabolized. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects.

After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) and to a lesser extent

in the urine (approximately 13% of the administered oral dose). Similar values for pharmacokinetic parameters were seen in normal volunteers and in the patient population, using a population pharmacokinetic approach.

Pharmacokinetics in Special Populations

Geriatrics: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 84% and 107% higher plasma AUC values of sildenafil and its active N-desmethyl metabolite, respectively, compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in the AUC of free (unbound) sildenafil and its active N-desmethyl metabolite were 45% and 57%, respectively.

Renal Impairment: In volunteers with mild (CLcr=50-80 mL/min) and moderate (CLcr=30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of PLS NAYGRA 100 (50 mg) were not altered. In volunteers with severe (CLcr <30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment.

In addition, N-desmethyl metabolite AUC and C_{max} values significantly increased by 200% and 79%, respectively in subjects with severe renal impairment compared to subjects with normal renal function.

Hepatic Impairment: In volunteers with hepatic impairment (Child-Pugh Class A and B), sildenafil clearance was reduced, resulting in increases in AUC (85%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child-Pugh Class C) have not been studied.

5.3 PRECLINICAL SAFETY DATA

Carcinogenesis Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUCs) for unbound sildenafil and its major metabolite of 29-and 42-times, for male and female rats, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg. Sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m^2 basis.

Mutagenesis Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

Impairment of Fertility There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males, a dose producing an AUC value of more than 25 times the human male AUC.

6.PHARAMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

S.N.	Excipients	Specification
1	Micro crystallin cellulose	BP
2	Dicalcium phosphate	BP
3	Povidone	BP
4	Isopropyl alcohol	BP
5	Magnesium stearate	BP
6	Purified talc	BP
7	Colloidal anhydrous silica	BP
8	Croscarmellose sodium	BP
9	Ready coat-blue (Brilliant blue FCF)	INH
10	Purified water	BP

BP: British Pharmacopoeia
INH: IN- House Specification

6.2 INCOMPATIBILITY

None such data reported.

6.3 SHELF LIFE

36 months (3 years)

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

1x4 Alu-PVC

6.6 SPECIAL PRECAUTIONS FOR DISPOSABLE AND OTHER HANDLING

None such special precautions for disposing and handling applies for this product.

7. MARKET AUTHORIZATION HOLDER AND MANUFACTURING SITE

Market Authorization Holder**:**
PHARMA LIFE SCIENCE
P.O.Box: 38148-00623
Nairobi, KENYA

Manufactured By:
FREDUN PHARMACEUTICALS LTD.
14,15,16, Zorabian Industrial Complex,
Vevoor, Palghar (E)-401404. INDIA.

8. MARKET AUTHORIZATION NUMBER

Not Applicable

9. DATE OF FIRST REGISTRATION / RENEWAL REGISTRATION

Not Applicable

10. DATE OF REVISION OF TEXT

Not Applicable

11. DOSIMETRY (IF APPLICABLE)

Not Applicable

12. INSTRUCTION FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable