1. NAME OF THE MEDICINAL PRODUCT

UPGRA FORTE 100 (Sildenafil Citrate Tablets 100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each film coated tablet contains:

Sildenafil Citrate

Equivalent to Sildenafil 100 mg

Cooler: Brilliant Blue FCF, Titanium Dioxide BP

Excipients: q. s.

Batch Size: 100000 Tablet

Sr. No	Ingredients	Spec.	Qty/ Tab (mg)	Ovg.	Qty/ Batch (gm)	Function
1	Sildenafil Citrate Equivalent to Sildenafil	IHS	140.480 ≡ 100.000	--	14.048	Active
2	Microcrystalline Cellulose (Avicel pH 102)	BP	249.400	--	24.940	Diluent
3	Dicalcium Phosphate (Anhydrous)	BP	120.520	--	12.052	Diluent
4	Povidone (P.V.P. K-30)	BP	16.000	--	1.600	Binder
5	Isopropyl Alcohol	BP	250.000	--	25.000	Solvent
LUBRICATION						
6	Magnesium Stearate	BP	10.000	--	1.000	Lubricant
7	Purified Talc	BP	9.000	--	0.900	Coating agent
8	Colloidal Anhydrous Silica	BP	4.600	--	0.460	Disintegrant
9	Croscarmellose Sodium	BP	22.000	--	2.200	Disintegrant
10	Microcrystalline Cellulose (Avicel pH 102)	BP	10.000	--	1.000	Diluent
		Total	**582.00**			
FILM COATING						
11	Readycoat AMB (Brilliant blue lake) 58N0030139	IHS	18.000	--	1.800	Coating agent
12	Purified Water	BP	68.650	--	6.865	Solvent
		Total	**600.00**			

BP : British Pharmacopoeia IHS : In-house Specification

Average weight of uncoated tablet : 582.00 mg ± 5.0%

Average weight of film coated tablet : 600.00 mg ± 5.0%

3. PHARMACEUTICAL FORM

Film coated tablets

Light blue colored, Diamond Shaped, biconvex, film coated tablets with “100” embossed on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

1. For the treatment of erectile dysfunction.
2. For the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability

4.2 Posology and method of administration

Route of administration: Oral

Average duration of treatment

The recommended dose of sildenafil is 20 mg three times a day (t.i.d.). Sildenafil tablets should be taken approximately 4-6 hours apart, with or without food. Treatment with doses higher than 20 mg t.i.d. is not recommended.

Dosage in special situations e.g., renal, hepatic, and cardiac insufficiency

The following factors are associated with increased plasma levels of sildenafil: age >65 (40% increase in AUC), hepatic impairment (e.g., cirrhosis, 80%), severe renal impairment (creatinine clearance <30 mL/min, 100%), and concomitant use of potent cytochrome P450 3A4 inhibitors [ketoconazole, itraconazole, erythromycin (182%), saquinavir (210%)]. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.

It greatly increased the systemic level of sildenafil in a study of healthy, non-HIV infected volunteers. Based on these pharmacokinetic data, it is recommended not to exceed a maximum single dose of 25 mg in a 48-hour period.

4.3 Contraindications

i) Use of Sildenafil Citrate is contraindicated in patients with a known hypersensitivity to any component of the tablet.

ii) Consistent with its known effects on the nitric oxide/cGMP pathway, Sildenafil

Citrate was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated.

iii)In the following patients: age >65, hepatic impairment (e.g., cirrhosis), severe renal impairment (e.g., creatine clearance <30 mL/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (e.g., erythromycin); plasma levels of sildenafil, at 24 hours post dose, have been found to be 3 to 8 times higher than those seen in healthy volunteers.

4.4 Special warnings and precautions for use

Warnings

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A4 inhibitor) substantially increases serum concentrations of Sildenafil; therefore, co-administration is not recommended.

It has vasodilator properties, resulting in mild and transient decreases in blood pressure. Prior to prescribing, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilator effects, for example patients with resting hypotension (BP <90/50), or with fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction.

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration to patients with veno-occlusive disease, administration to such patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

There is no controlled clinical data on the safety or efficacy in the following groups; if prescribed, this should be done with caution:

1. Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months.
2. Patients with coronary artery disease causing unstable angina.
3. Patients with hypertension (BP >170/110).
4. Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterase's).

Precautions

General

Before prescribing, it is important to note the following:

1. Caution is advised when phosphodiesterase type 5 (PDE5) inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including sildenafil, 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, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported. No cases of syncope or fainting were reported during these interaction studies. Consideration should be given to the fact that safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

2. It 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). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erections greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result

3. In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

4. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%). The incidence of epistaxis was also higher in sildenafil-treated patients with concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).

5. The safety is unknown in patients with bleeding disorders and patients with active peptic ulceration.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sildenafil

In vitro studies:

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance

In vivo studies:

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25 mg should be considered.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/ml, compared to approximately 5 ng/ml when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised and, in any event, the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours.

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil Cmax and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, Cmax, tmax, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of sildenafil.

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component, it has the potential to have serious interaction with sildenafil.

Effects of sildenafil on other medicinal products

In vitro studies:

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 > 150 µM). Given sildenafil peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely that Sildenafil tablets will alter the clearance of substrates of these isoenzymes.

There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies:

Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated

Riociguat: Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favorable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated.

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. In three specific drug-drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

No significant interactions were shown when sildenafil (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.

Pooling of the following classes of antihypertensive medication: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally acting), adrenergic neuron blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteer.

4.6 Pregnancy and Lactation

Pregnancy

Sildenafil tablets is not indicated for use by women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to Sildenafil before driving or operating machinery.

4.8 Undesirable effects

Cardiovascular

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, and hypertension. 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 Sildenafil Citrate without sexual activity. Others were reported to have occurred hours to days after the use of Sildenafil Citrate and sexual activity. It is not possible to determine whether these events are related directly to Sildenafil Citrate, to sexual activity, to the patient underlying cardiovascular disease, to a combination of these factors, or to other factors.

Ocular:

Abnormal vision (Mild and transient. Predominantly color tinge to vision, but also increased perception of light or blurred vision). Diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular edema. Conjunctivitis, photophobia, eye hemorrhage, cataract, dry eyes and eye pain.

Urogenital:

Cases of priapism (prolonged erection) have been reported. Cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema, anorgasmia and haematuria have also been reported.

Body as a whole:

Face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Digestive:

Dyspepsia, 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, and hypernatremia.

Musculoskeletal:

Arthritis, arthrosis, myalgia, tendon rupture, and tenosynovitis, bone pain, myasthenia, synovitis.

Nervous:

Ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, and hypesthesia.

Respiratory:

Nasal congestion, asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and Appendages:

Urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

4.9 Overdose

Brief clinical description of symptoms

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

Treatment of over dosage

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 group: Drugs used in erectile dysfunction.

ATC code: G04B E03.

Mechanism of action:

Sildenafil is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE5) in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary hypertension, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Studies in vitro have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterase's (10-fold for PDE6, >80-fold for PDE1, >700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11).

In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE5 is also found in other tissues including vascular and visceral smooth muscle and in platelets. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity of nitric oxide observed in vitro, and the mild peripheral arterial-venous dilatation in vivo.

5.2 Pharmacokinetic properties

Absorption & Distribution

Sildenafil is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. 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 Tmax of 60 minutes and a mean reduction in Cmax 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-dimethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Metabolism and Excretion

Sildenafil is cleared predominantly by the CYP3A4 (major route) and cytochrome P450 2C9 (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 phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. In healthy volunteers, 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. In patients with pulmonary arterial hypertension, however, the ratio of the metabolite to sildenafil is higher. Both sildenafil and the active metabolite have terminal half-lives of about 4 hours. The concomitant use of potent cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S.No.	Excipients	Specifications
1	Microcrystalline Cellulose (Avicel pH 102)	As per BP
2	Dicalcium Phosphate (Anhydrous)	As per BP
3	Povidone (P.V.P. K-30)	As per BP
4	Isopropyl Alcohol	As per BP
5	Magnesium Stearate	As per BP
6	Purified Talc	As per BP
7	Colloidal Anhydrous Silica	As per BP
8	Croscarmellose Sodium	As per BP
9	Readycoat AMB (Brilliant blue lake)	As per IHS
10	Purified Water	As per BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months (3 years)

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture.

6.5 Nature and contents of container <and special equipment for use, administration, or implantation>

Alu/ PVC Blister pack of 4 Tablets, such 4 blisters packed in one mono carton along with leaflet. And such 25 mono carton packed in one outer carton.

Sr. No.	**Container closure system / Blister pack of 4 tablets.**
Primary Packing	
1.	Printed aluminium foil
2.	PVC film
Secondary Packing	
3.	Printed carton
4.	Leaflet
5.	7 ply corrugated shipper

6.6 Special precautions for disposal <and other handling>

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

APPLICANT :

PREFFRRED DRUGD NIGERIA LTD.

Address: 20 Erhuvwa Club Street, Asaba Delta State,
Nigeria & Preferred Groups LLC, Maryland U.S.A
www.preferred-drugs.com

MANUFACTURER:

FREDUN PHARMACEUTICAL LTD.

Address: 14,15,16,Zorabian Indl. Complex,
Vevoor, Palghar-401404, Maharashtra state, India.
Contact No.: Phone: 91-22-40318111
Email: business@fredungroup.com

Marketing authorization number

Date of first registration/renewal of the registration

-Not applicable.

Date of revision of the text

-Not applicable.