SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

TADALAFIL TABLETS USP 20 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each film coated tablet contains:

Tadalafil USP 20 mg

Excipients: q.s.

Colour: Iron Oxide Yellow, Titanium dioxide BP

Sr. No.	Ingredients	Spec.	Qty. / Tab (mg)	Ovg.	Reason for inclusion
1.	Tadalafil	USP	20.000	--	Active
2.	Microcrystalline Cellulose (pH 102)	BP	103.000	--	Disintegrant
3.	Lactose Monohydrate	BP	80.000	--	Diluent
4.	Hydroxy Propyl Cellulose	BP	8.000	--	Binder
5.	* Isopropyl Alcohol	BP	QS	--	Solvent
	Lubricants				
6.	Poloxamer 188	USP	5.000	--	Lubricant
7.	Magnesium Stearate	BP	4.000	--	Lubricant
8.	Colloidal Anhydrous Silica	BP	2.000	--	Glidant
9.	Crospovidone	BP	66.000	--	Disintegrant
	TOTAL		**289.000**		
	Film Coating				
10.	Hypromellose (E – 15)	BP	4.000	--	Film-former
11.	Titanium Dioxide	BP	1.500	--	Colouring agent
12.	Iron Oxide Yellow	IH	0.200	--	Colouring agent
13.	Purified Talc	BP	1.800	--	Glidant
14.	Propylene Glycol	BP	0.250	--	Plasticizer
15.	Macrogols – 4000	BP	0.250	--	Plasticizer
16.	* Isopropyl Alcohol	BP	QS	--	Solvent
17.	* Purified Water	IH	QS	--	Solvent
	TOTAL		**297.000**		

* Isopropyl alcohol and Purified water are used as solvent and not found in the final product.

USP: United State Pharmacopoeia

BP: British Pharmacopoeia

IH: In House Specification

Average weight of compressed tablet: 289.00 mg ± 5.0 %

Average weight of coated tablet : 297.00 mg ± 5.0 %

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of erectile dysfunction in adult males.

(In order for Tadalafil to be effective for the treatment of erectile dysfunction, sexual stimulation is required) 5 mg only: Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.

4.2 Posology and Method of Administration

Erectile dysfunction in adult men

In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food. In those patients in whom Tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10mg and 20mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use (i.e., at least twice weekly) a once daily regimen with the lowest doses might be considered suitable, based on patient choice and the physician's judgment.

In these patients, the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Benign prostatic hyperplasia in adult men

The recommended dose is 5 mg, taken at approximately the same time every day with or without food. For adult men being treated for both benign prostatic hyperplasia and erectile dysfunction the recommended dose is also 5 mg taken at approximately the same time every day. Patients who are unable to tolerate Tadalafil 5 mg for the treatment of benign prostatic hyperplasia should consider an alternative therapy as the efficacy of Tadalafil 2.5mg for the treatment of benign prostatic hyperplasia has not been demonstrated.

Special populations

Elderly men

Dose adjustments are not required in elderly patients.

Men with renal impairment

Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment, 10mg is the maximum recommended dose for on-demand treatment.

Paediatric population

There is no relevant use of Tadalafil in the paediatric population with regard to the treatment of erectile dysfunction.

4.3 Contraindications

i) Hypersensitivity to the active substance or to any of the excipients.

ii) In clinical studies, Tadalafil was shown to augment the hypotensive effects of nitrates because of combined effects of nitrates and Tadalafil on the nitric oxide/Cgmp pathway. Therefore, administration to patients who are using any form of organic nitrate is contraindicated.

iii) It must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

iv) The following groups of patients with cardiovascular disease were not included in clinical trials and the use of Tadalafil is therefore contraindicated:

• Patients with myocardial infarction within the last 90 days.

• Patients with unstable angina or angina occurring during sexual intercourse.

• Patients with New York Heart Association class 2 or greater heart failure in the last 6 months.
• Patients with uncontrolled arrhythmias, hypotension (<90/50mmHg), or uncontrolled hypertension.
• Patients with a stroke within the last 6 months.

4.4 Special Warnings and Precautions for use

i) A medical history and physical examination should be undertaken to diagnose erectile dysfunction or benign prostatic hyperplasia and determine potential underlying causes, before pharmacological treatment is considered.

ii) Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure and as such potentiates the hypotensive effect of nitrates.

iii) Prior to initiating treatment with Tadalafil for benign prostatic hyperplasia patients should be examined to rule out the presence of carcinoma of the prostate and carefully assessed for cardiovascular conditions

iv) Tadalafil (2.5mg and 5mg) - In patients receiving concomitant antihypertensive medicinal products, Tadalafil may induce a blood pressure decrease. When initiating daily treatment with Tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

v) In patients who are taking alpha1 blockers, concomitant administration may lead to symptomatic hypotension in some patients. E.g. Doxazosin

4.5 Interaction with other medicinal products and other forms of interaction

i) Since PDE5 inhibitors such as Tadalafil may cause transiently low blood pressure (hypotension), organic nitrates should not be taken for at least 48 hours after taking the last dose of Tadalafil. Using organic nitrites (such as the sex drug amyl nitrite) within this timeframe may increase the risk of life-threatening hypotension.

ii) Since people who have taken Tadalafil within the past 48 hours cannot take organic nitrates to relieve angina (such as glyceryl trinitrate spray), these patients should seek immediate medical attention if they experience anginal chest pain. In the event of a medical emergency,
paramedics and medical personnel should be notified of any recent doses of Tadalafil.

iii) Tadalafil is metabolized predominantly by the hepatic CYP3A4 enzyme system. The presence of other drugs which induce this system can shorten Tadalafil half-life and reduce serum levels, and hence efficacy, of the drug.

4.6 Pregnancy and Lactation

i) Tadalafil is not indicated for use by women.

ii) There are limited data from the use of Tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use during pregnancy.

4.7 Effects on ability to drive and use machines

Tadalafil has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to Tadalafil, before driving or using machines.

4.8 Undesirable Effects

The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Immune system disorders:

Uncommon : Hypersensitivity reactions

Rare : Angioedema

Nervous system disorders:

Common : Headache

Uncommon : Dizziness

Rare : Stroke

Eye disorders:

Uncommon : Blurred vision, Sensations as eye pain

Rare : Visual field defect, swelling of eyelids,

Conjunctival hyperaemia, Non – arteritic anterior ischemic

optic neuropathy (NAION), Retinal vascular occlusion

Ear and labyrinth disorders:

Uncommon : Tinnitus

Rare : Sudden hearing loss

Cardiac disorders:

Uncommon : Tachycardia, Palpitation

Rare : Myocardial infarction, unstable angina pectoris, ventricular arrythmia

Vascular disorders:

Common : Flushing

Uncommon : Hypotension, Hypertension

Respiratory, Thoracic and mediastinal disorders:

Common : Nasal congestion, Abdominal pain

Uncommon : Dyspnoea, Epitaxis

Gastro intestinal disorders:

Common : Dyspepsia, Gastro-oesophageal reflux

Uncommon : Abdominal pain

Skin and subcutaneous tissue disorders:

Uncommon : Haematuria

Musculoskeletal, connective tissue and bone disorders:

Common : Back pain, Myalgia, Pain in extremity

Reproductive disorders and breast disorders:

Uncommon : Penile haemorrhage, haematospermia

Rare : Prolonged erections, priapism

General disorders and administration site conditions:

Uncommon : Chest pain

Rare : Facial oedema, sudden cardiac death

4.9 Overdose

i) Single doses of up to 500mg have been given to healthy subjects, and multiple daily doses up to 100mg have been given to patients. Adverse events were similar to those seen at lower doses.

ii) In cases of overdose, standard supportive measures should be adopted, as required. Haemodialysis

contributes negligibly to Tadalafil elimination.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Therapeutic category: Drug used in erectile dysfunction

Mechanism of action

i) Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP) - specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by Tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the treatment of erectile dysfunction in the absence of sexual stimulation.

ii) The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The resulting vascular relaxation increases blood perfusion which may be the mechanism by which symptoms of benign prostatic hyperplasia are reduced. These vascular effects may be complemented by inhibition of bladder afferent nerve activity and smooth muscle relaxation of the prostate and bladder.

5.2 Pharmacokinetic Properties

Absorption

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food, thus Tadalafil may be taken with or without food. The time of dosing (morning versus evening after a single 10 mg administration) had no clinically relevant effects on the rate and extent of absorption.

Distribution

The mean volume of distribution is approximately 63 liters, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation

Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination

The mean oral clearance for tadalafil is 2.5 L/h and the mean half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

There was no evidence of teratogenicity, embryotoxicity, or foetotoxicity in rats or mice that received up to 1000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18-times the human AUC at a 20 mg dose.

There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7-18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sr. No.	Name of Raw Material	Specification
1.	Microcrystalline cellulose	BP
2.	Lactose Monohydrate	BP
3.	Hydroxy propyl cellulose	BP
4.	Isopropyl alcohol	BP
5.	Poloxamer 188	USP
6.	Magnesium stearate	BP
7.	Colloidal anhydrous silica	BP
8.	Crospovidone	BP
9.	Hypromellose (E – 15)	BP
10.	Titanium dioxide	BP
11.	Iron Oxide Yellow	IH
12.	Purified Talc	BP
13.	Propylene glycol	BP
14.	Macrogols – 4000	BP
15.	Purified Water	IH

6.2 Incompatibilities

None

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store in cool and dry place beow 30°C

6.5 Nature and contents of container

Blister Pack of 4 Tablets

6.6 Special precautions for disposal and other handling

No special requirement

7. HOLDER OF THE MARKETING AUTHORIZATION

Lynedge Phrmaceutical Limited, Chevron Alternative road, lekki, lagos.

8. MARKETING AUTHORIZATION NUMBER (S)

1) 20B/MH-TZ4-393625

2) 21B/MH-TZ4-393626

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF AUTHORIZATION

1) 20B/MH-TZ4 - 06. Nov-2020 to 05. Nov-2025

2) 21B/MH-TZ4 - 06. Nov-2020 to 05. Nov-2025

10. DATE OF REVISION OF THE TEXT

As per revision

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