SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	Product Name : **APCALIS-SX 10 (**Tadalafil Tablets USP 10 mg**)** **APCALIS-SX 20 (**Tadalafil Tablets USP 20 mg**)**
	1.2 Strength : **APCALIS-SX 10 (**Tadalafil Tablets USP 10 mg**)** Each film coated tablet contains: - Tadalafil USP (10 mg) **APCALIS-SX 20 (**Tadalafil Tablets USP 20 mg**)** Each film coated tablet contains: - Tadalafil USP (20 mg)
	1.3 Pharmaceutical Dosage Form : Tablet
2.	**Qualitative & Quantitative Composition:** **APCALIS-SX 10 (**Tadalafil Tablets USP 10 mg**)** Each film coated tablet contains: - Tadalafil USP (10 mg) - Colour: Yellow Oxide of Iron and Titanium Dioxide (-) **APCALIS-SX 20 (**Tadalafil Tablets USP 20 mg**)** Each film coated tablet contains: - Tadalafil USP (20 mg) - Colour: Yellow Oxide of Iron and Titanium Dioxide (-) For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:**
	Tablet Pale yellow coloured, elliptical shaped, film coated tablets, plain on both sides.
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: Tadalafil is indicated in the treatment of erectile dysfunction in adult males. In order for tadalafil to be effective for the treatment of erectile dysfunction, sexual stimulation is required. Tadalafil is not indicated for use by women.
	4.2 Posology and Method of administration: Posology *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 10 mg and 20 mg is intended for use prior to anticipate sexual activity and it is not recommended for continuous daily use. In patients who anticipate a frequent use of Tadalafil (i.e., at least twice weekly) a once daily regimen with the lowest doses of Tadalafil might be considered suitable, based on patient choice and the physician's judgement. The appropriateness of continued use of the daily regimen should be reassessed periodically. 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, 10 mg is the maximum recommended dose. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment. *Men with hepatic impairment* The recommended dose of Tadalafil is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of Tadalafil in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of Tadalafil to patients with hepatic impairment. Once-a-day dosing has not been evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. *Men with diabetes* Dose adjustments are not required in diabetic patients. *Paediatric population* There is no relevant use of Tadalafil in the paediatric population with regard to the treatment of erectile dysfunction. *Method of administration* Tadalafil for oral use.
	4.3 Contraindications: Hypersensitivity to the active substance or to any of the excipients. In clinical studies, Tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and Tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated.

	Tadalafil 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. 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 (< 90/50 mm Hg), or uncontrolled hypertension, - Patients with a stroke within the last 6 months. Tadalafil is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure. The co-administration of PDE5 inhibitors, including Tadalafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.
	4.4 Special warning and precautions for use: Hypersensitivity to the active substance or to any of the excipients. In clinical studies, Tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and Tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated. Tadalafil 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. 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 (< 90/50 mm Hg), or uncontrolled hypertension, - Patients with a stroke within the last 6 months.

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	4.5 Interactions with other medicinal products and other forms of Interactions : Interaction studies were conducted with 10 mg and/or 20 mg Tadalafil, as indicated below. With regard to those interaction studies where only the 10 mg Tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out. <u>Effects of other substances on Tadalafil</u> *Cytochrome P450 inhibitors* Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased Tadalafil (10 mg) exposure (AUC) 2-fold and Cmax by 15 %, relative to the AUC and Cmax values for Tadalafil alone. Ketoconazole (400 mg daily) increased Tadalafil (20 mg) exposure (AUC) 4-fold and Cmax by 22 %. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased Tadalafil (20 mg) exposure (AUC) 2-fold with no change in Cmax. Although specific interactions have not been studied, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice should be co-administered with caution as they would be expected to increase plasma concentrations of Tadalafil. *Transporters* The role of transporters (for example p-glycoprotein) in the disposition of Tadalafil is not known. Therefore there is the potential of drug interactions mediated by inhibition of transporters. *Cytochrome P450 inducers* A CYP3A4 inducer, rifampicin, reduced Tadalafil AUC by 88 %, relative to the AUC values for Tadalafil alone (10 mg). This reduced exposure can be anticipated to decrease the efficacy of Tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of Tadalafil. <u>Effects of Tadalafil on other medicinal products</u> *Nitrates* In clinical studies, Tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated. Based on the results of a clinical study in which 150 subjects received daily doses of Tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last Tadalafil dose. Thus, in a patient prescribed any dose of Tadalafil (2.5 mg-20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed

after the last dose of Tadalafil before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8 mg daily) and Tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended.

In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However, caution should be exercised when using Tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

In patients receiving concomitant antihypertensive medicinal products, Tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers -see above-) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

Riociguat
Concomitant use of riociguat with PDE5 inhibitors, including Tadalafil, is contraindicated.

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is coadministered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
When Tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by coadministration with Tadalafil (10 mg or 20 mg). In addition, no changes in Tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was

	administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol).Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40 % alcohol [vodka] in an 80-kg male) but in some subjects, postural dizziness and orthostatic hypotension were observed. When Tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by Tadalafil (10 mg). *Cytochrome P450 metabolised medicinal products* Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products metabolised by CYP450 isoforms. Studies have confirmed that Tadalafil does not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19. *CYP2C9 substrates (e.g. R-warfarin)* Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did Tadalafil affect changes in prothrombin time induced by warfarin. *Aspirin* Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid. *Antidiabetic medicinal products* Specific interaction studies with antidiabetic medicinal products were not conducted.
	4.6 Pregnancy and Lactation: Tadalafil is not indicated for use by women. <u>Pregnancy</u> 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 of Tadalafil during pregnancy. <u>Breastfeeding</u> Available pharmacodynamic/toxicological data in animals have shown excretion of Tadalafil in milk. A risk to the suckling child cannot be excluded. Tadalafil should not be used during breast feeding.
	4.7 Effects on ability to drive and use machine: 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: <u>Summary of the safety profile</u>

The most commonly reported adverse reactions in patients taking Tadalafil for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of Tadalafil. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with Tadalafil once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated summary of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo controlled clinical trials (comprising a total of 8022 patients on Tadalafil and 4422 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a- day treatment of benign prostatic hyperplasia.

Frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) and not known (cannot be estimated from the available data).

Very common	Common	Uncommon	Rare
Immune system disorders			
		Hypersensitivity reactions	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures[2], Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischaemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]

	Vascular disorders			
		Flushing	Hypotension[3], Hypertension	
	Respiratory, thoracic and mediastinal disorders			
		Nasal congestion	Dyspnoea, Epistaxis	
	Gastrointestinal disorders			
		Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux	
	Skin and subcutaneous tissue disorders			
			Rash	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis (sweating)
	Musculoskeletal, connective tissue and bone disorders			
		Back pain, Myalgia, Pain in extremity		
	Renal and urinary disorders			
			Haematuria	
	Reproductive system and breast disorders			
			Prolonged erections	Priapism, Penile haemorrhage, Haematospermia
	General disorders and administration site conditions			
			Chest pain[1], Peripheral oedema, Fatigue	Facial oedema[2], Sudden cardiac death[1,2]

(1) Most of the patients had pre-existing cardiovascular risk factors.
(2) Post marketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) More commonly reported when Tadalafil is given to patients who are already taking antihypertensive medicinal products.

	4.9 Overdosage: Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to Tadalafil elimination.
5.	**Pharmacological properties**

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction

Mechanism of action

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.

Pharmacodynamic effects

Studies *in vitro* have shown that Tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of Tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is >10,000fold more potent for PDE5 than for PDE1, PDE2, and PDE4 enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is >10,000fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, Tadalafil is approximately 700 fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also >10,000 fold more potent for PDE5 than for PDE7 through PDE10.

5.2 Pharmacokinetics 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) had no clinically relevant effects on the rate and extent of absorption.

Distribution

The mean volume of distribution is approximately 63 litres, 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: Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Sodium Lauryl Sulfate, Low - Substituted Hydroxypropyl Cellulose, Magnesium Stearate, Instacoat Sol IC-S-1179 and Purified Water
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 24 months
	6.4 Special Precautions for storage: Store below 30°C. Protect from light.
	6.5 Nature and contents of container: 2 tablets in Alu- PVC blister pack, 2 such blisters are packed in a carton along with Patient Information Leaflet.
	6.6 Special precautions for disposal: Not applicable
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India **Manufacturing Site Address:** Ajanta Pharma Limited B-4/5/6, M.I.D.C. Area, Paithan, Dist. Aurangabad,

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8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** Nov 18, 2019