Tastylia® 20 mg

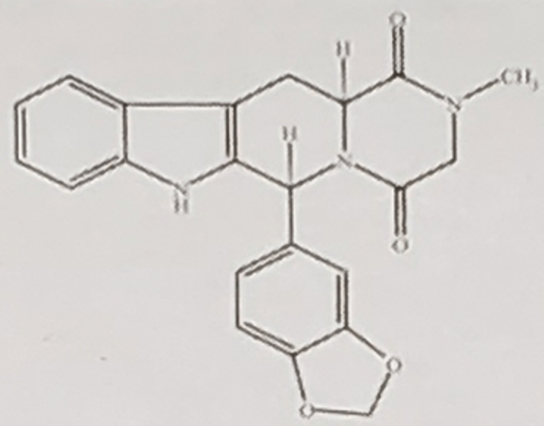
Tadalafil 20mg

Composition
Each orally disintegrating strip contains:
Tadalafil 20 mg
Color: Approved Color

DESCRIPTION:
Pink colored strips

CHEMICAL NAME:
Pyrazino[1´,2´:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexa hydro- 2-methyl-, (6R,12aR)
Molecular formula and molecular mass: C22H19N3O4; 389.41

STRUCTURAL FORMULA:



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

PHARMACODYNAMICS
Oral dose of Tadalafil 20mg produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6mm Hg, respectively). There was no significant effect on heart rate

Effects of Tadalafil on Sperm Motility:
Tadalafil had no effect on sperm motility, morphology, concentrations. There was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20mg of tadalafil compared to placebo.

PHARMACOKINETICS
When administered orally to healthy male volunteers, tadalafil was rapidly absorbed, with maximum observed plasma concentrations (Cmax) occurring 0.5-2 hours after dosing in most subjects. Cmax and areas under the plasma concentration time curve increased in a proportional manner with dose over the clinical dose.

Tadalafil has an apparent volume of distribution 63 litres, indicating that tadalafil is distributed into tissues. Approximately 94% of tadalafil is bound to plasma proteins. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism and Elimination
Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

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

INDICATIONS AND USAGE
TASTYLIA is indicated for: The treatment of erectile dysfunction, the signs and symptoms of benign prostatic hyperplasia and both erectile dysfunction and the signs and symptoms of benign prostatic hyperplasia.

CONTRAINDICATIONS
Administration of Tadalafil to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, Tadalafil was shown to potentiate the hypotensive effect of nitrates. Tadalafil is contraindicated in patients with a known serious hypersensitivity to tadalafil. Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis. Do not use Tadalafil in patients who are using a GC (Concomitant Guanylate Cyclase) stimulator, such as riociguat. PDE5 inhibitors, including Tadalafil, may potentiate the hypotensive effects of GC stimulators.

Treatments for erectile dysfunction should not be generally used in men for whom sexual activity is inadvisable.

PRECAUTIONS
General
The evaluation of erectile dysfunction and BPH should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options. Before prescribing TASTYLIA, it is important to note the following:

Cardiovascular
As with all treatments for erectile dysfunction, there is a potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for erectile dysfunction, including TASTYLIA, should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status.

Potential for Drug Interactions When Taking Tastylia for Once Daily Use
Physicians should be aware that TASTYLIA for once daily use provides continuous plasma tadalafil levels and should consider this when evaluating the potential for interactions with medications (e.g., nitrates, alpha-blockers, antihypertensives and potent inhibitors of CYP3A4) and with substantial consumption of alcohol.

Prolonged Erection
TASTYLIA should be used with caution in patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

Effects on the Eye
Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including TASTYLIA, and seek medical attention in the event of a sudden loss of vision in one or both eyes.

Sudden Hearing Loss
Physicians should advise patients to stop taking PDE5 inhibitors, including TASTYLIA, and seek prompt medical attention in the event of sudden decrease or loss of hearing.

Alpha-blockers and Antihypertensives
Physicians should discuss with patients the potential for TASTYLIA to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications.

Renal Impairment
The starting dose of Tadalafil in patients with creatinine clearance 30–50mL/min should be 5mg not more than once per day, and the maximum dose should be limited to 10mg not more than once in every 48 hours

Hepatic Impairment
The dose of Tadalafil should not exceed 10mg in patients with mild or moderate hepatic impairment.

Alcohol
Alcohol and Tadalafil can result an increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Concomitant Use of Potent Inhibitors of Cytochrome P450 3A4 (CYP3A4)
The dose of Tadalafil for use as needed should be limited to 10mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, and itraconazole.

Combination with other PDE5 Inhibitors or Erectile Dysfunction Therapies
Patients should not take Tadalafil with other PDE5 inhibitors, including ADCIRCA.

Effects on Bleeding
When administered in combination with aspirin, Tadalafil 20mg did not prolong bleeding time, relative to aspirin alone. Tadalafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although Tadalafil has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

Counseling Patients about Sexually Transmitted Diseases
The use of Tastylia offers no protection against sexually transmitted diseases. Counseling patients about the protective measures necessary to guard against sexually transmitted diseases, including Human

ADVERSE REACTIONS

The adverse events were generally transient and mild to moderate in nature. In fixed dose studies, the incidence of some adverse events increased with dose.

The most commonly reported adverse reactions were headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, pain in limb, see table 1 below:

Table 1: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with Tadalafil (10 or 20mg) and More Frequent on Drug than Placebo in the Eight Primary Placebo-Controlled Clinical Studies (Including a Study in Patients with Diabetes) for Tadalafil for Use as Needed for ED

The term flushing includes: facial flushing and flushing

Adverse Reaction	Placebo (N=476)	Tadalafil 5mg (N=151)	Tadalafil 10mg (N=349)	Tadalafil 20mg (N=635)
Headache	5%	11%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal congestion	1%	2%	3%	3%
Flushing*	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

DRUG INTERACTIONS

Potential for Pharmacodynamic Interactions with Tadalafil

Administration of TASTYLIA to patients who are using any form of organic nitrate is contraindicated. Caution is advised when PDE5 inhibitors including Tadalafil are coadministered with alpha-blockers. Small reductions in blood pressure occurred following coadministration of Tadalafil with antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and metoprolol). Alcohol and Tadalafil can increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Potential for other Drugs to affect Tadalafil

Antacids: Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

H2 Antagonists (e.g. Nizatidine): An increase in gastric pH resulting from administration of nizatidine had no significant effect on pharmacokinetics.

Cytochrome P450 Inhibitors: Tadalafil is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure.

HIV Protease inhibitor: Ritonavir (500mg or 600mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in Cmax, relative to the values for tadalafil 20mg alone. Ritonavir (200mg twice daily), increased tadalafil 20-mg single-dose exposure (AUC) by 124% with no change in Cmax, relative to the values for tadalafil 20mg alone.

Cytochrome P450 Inducers: Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure. CYP3A4 (e.g., Rifampin) — Rifampin (600mg daily), a CYP3A4 inducer, reduced tadalafil 10-mg single-dose exposure (AUC) by 88% and Cmax by 46%, relative to the values for tadalafil 10mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted. The reduced exposure of tadalafil with the coadministration of rifampin or other CYP3A4 inducers can be anticipated to decrease the efficacy of Tadalafil for once daily use; the magnitude of decreased efficacy is unknown.

Potential for Tadalafil to affect other drugs

Aspirin: Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

CYP1A2 (e.g. Theophylline): Tadalafil had no significant effect on the pharmacokinetics of theophylline. When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP2C9 (e.g. Warfarin): Tadalafil had no significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin.

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CYP3A4 (e.g. Midazolam or Lovastatin): Tadalafil had no significant effect on exposure (AUC) to midazolam or lovastatin.

P-glycoprotein (e.g. Digoxin): Coadministration of tadalafil (40mg once per day) for 10 days did not have a significant effect on the steady-state pharmacokinetics of digoxin (0.25mg/day) in healthy subjects.

SPECIAL POPULATIONS

Women, Nursing Mothers, Pregnancy: Tadalafil is not indicated for use in women.

Pediatric Use

Tadalafil is not indicated for use in pediatric patients.

Geriatric Use

In ED clinical studies of tadalafil, no overall differences in efficacy or safety were observed between older (>65 and ≥75 years of age) and younger subjects (≤65 years of age). However, in placebo-controlled studies with Tadalafil for use as needed for ED, diarrhea was reported more frequently in patients 65 years of age and older who were treated with Tadalafil (2.5% of patients).

Hepatic Impairment

In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10mg was administered.

Renal Impairment

In a clinical pharmacology study (N=28) at a dose of 10mg, back pain was reported as a limiting adverse event in male patients with creatinine clearance 30 to 50mL/min.

OVERDOSAGE

Adverse events were similar for higher doses (single doses up to 500mg) and lower doses (multiple daily doses up to 100mg). In cases of overdose, standard supportive measures should be adopted as required.

DOSAGE AND ADMINISTRATION

Tadalafil for Use as Needed for Erectile Dysfunction

The recommended starting dose of Tadalafil for use as needed in most patients is 10mg, taken prior to anticipated sexual activity.

The dose may be increased to 20mg or decreased to 5mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.

Use with Food

T-film may be taken without regard to food.

ADMINISTRATION

To be taken as needed approximately 30-60 minutes before sexual activity. However, Tastylia may be anywhere from 0.5 hour to 4 hours before sexual activity. The maximum recommended dosing frequency is once per day. With dry hands, Peel back the foil backing and GENTLY remove the strip. IMMEDIATELY place the strip on top of the tongue where it dissolves in seconds, then swallow with saliva. Administration with liquid is not necessary.

DIRECTION FOR USAGE

Peel to open the pouch | Take the Strip Out | Place the Strip on the Tongue.

STORAGE CONDITIONS:

Store in a cool, dry and dark place; protect from moisture.

Keep the medicine out of reach of children.

Shelf Life: 2 years from the date of manufacture.

PRESENTATION:

10 Sachets packed in an inner with insert

Code No.: DRUGS/AP/18/2010

Marketed By:

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