CALIBERI

5 mg Orodispersible Film
20 mg Orodispersible Film

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Urological

Formulation
Each Orodispersible Film contains: Tadalafil 5 mg, and 20 mg respectively.

Product Description
Tadalafil Orodispersible Film (ODF) 5mg and 20mg are light yellow, rectangular orodispersible films.

Pharmacodynamics
Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction, ATC code: G04BE08

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 absence of sexual stimulation.

Pharmacokinetics
Tadalafil is well absorbed after an oral dose.
Tadalafil is widely distributed into tissues and is about 94% bound to plasma proteins. It is metabolized liver mainly by the cytochrome P450 isoenzyme CYP3A4. The major metabolite, the methylcatechol glucuronide, is inactive. The mean half-life of tadalafil is about 17.5 hours.
Tadalafil is excreted, mainly as metabolites, in the feces (61% of the dose), and to a lesser extent in the urine (36% of the dose). Clearance may be reduced in the elderly and in patients with renal impairment.

Mechanism of Action
- Benign prostatic hyperplasia

The exact mechanism of action of tadalafil in benign prostatic hyperplasia is not known, tadalafil selectively inhibits phosphodiesterase type 5 (PDE5) and increases cyclic guanosine monophosphate (cGMP) levels. The smooth muscle cells of the prostate, bladder and surrounding vasculature also contain PDE5; inhibiting PDE5 and increasing cGMP levels in these tissues may cause smooth muscle relaxation, as observed in the corpus cavernosum and pulmonary arteries.

- Erectile dysfunction

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosum smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cyclic guanosine monophosphate (GMP) 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 cyclic GMP. 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.

- Pulmonary hypertension

The inhibition of phosphodiesterase type 5 (PDE5) by tadalafil increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

Indications
Indicated for the management of benign prostatic hyperplasia, erectile dysfunction and pulmonary hypertension.

Dosage and Route of Administration
Tadalafil (Caliberi) orodispersible film is for oral administration. The film must be placed on the tongue and dissolved on the tongue. It must be immediately used once taken out from the pouch. It can be dissolved on the tongue without any water. Absorption is through the digestive tube.

Benign prostatic hyperplasia
- 5 mg orally once daily at the same time each day; for up to 26 weeks when used with finasteride for initiation of benign prostatic hyperplasia treatment

Benign prostatic hyperplasia - Erectile dysfunction
- 5 mg ORALLY once daily at the same time each day

Erectile dysfunction
- Once daily use: 2.5 mg ORALLY once daily at the same time each day; may increase to 5 mg ORALLY once daily based on efficacy and tolerability
- As needed use: 10 mg ORALLY prior to anticipated sexual activity; may increase to 20 mg ORALLY or decrease to 5 mg ORALLY based on efficacy and tolerability; maximum frequency is once daily

Pulmonary hypertension
- 40 mg orally once daily with or without food

Administration in hepatic impairment
Exposure to tadalafil in patients with mild to moderate hepatic impairment is comparable to healthy subjects when a dose of 10 mg is used. Regular daily dosing has not been evaluated.
- Mild to moderate hepatic impairment (Child-Pugh Class A or B): the maximum dose is 10 mg; regular daily dosing has not been evaluated
- Severe hepatic impairment (Child-Pugh Class C): insufficient data are available; in the UK, caution is advised, and in the USA use in this group is not recommended

Administration in renal impairment
The clearance of tadalafil is reduced in renal impairment.
In the UK, licensed product information recommends the following:
- Mild to moderate renal impairment: no dose adjustment
- Severe renal impairment: the maximum dose is 10 mg; regular daily dosing is not recommended in these patients

In the USA, the dose recommendations for tadalafil, when used as needed, in patients with renal impairment based on creatinine clearance (CC) are:
- Mild (CC 51 to 80 mL/minute): no dose adjustment
- Moderate (CC 31 to 50 mL/minute): an initial dose of 5 mg not more than once daily, with a maximum dose of 10 mg in 48 hours
- Severe (CC less than 30 mL/minute or on hemodialysis): a maximum dose of 5 mg not more than once in every 72 hours

For patients taking tadalafil on a regular daily basis:
- Mild (CC 51 to 80 mL/minute): no dose adjustment
- Moderate (CC 31 to 50 mL/minute): no dose adjustment
- Severe (CC less than 30 mL/minute or on hemodialysis): not recommended

High-altitude disorders
Hypoxic pulmonary hypertension associated with high altitude may respond to tadalafil.
A small study has shown some promising results in adults with a history of high-altitude pulmonary edema.

Although the use of tadalafil with an alpha blocker is not recommended in the UK, the combination may be used in the USA; in patients stabilized on alpha blocker therapy a starting dose of tadalafil 5 mg may be used. In patients taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole or ritonavir-boosted HIV-protease inhibitors, the dose of tadalafil when used as needed should not exceed 10 mg once every 72 hours; when used on a regular daily basis, the dose should not exceed 2.5 mg.

Contraindications
Contraindicated to patients using nitrates (any form) either regularly or intermittently. Contraindicated to patients concomitantly administered with a guanylate cyclase stimulator (e.g. riociguat). Should not be administered to patients with known hypersensitivity to tadalafil.

Warnings and Precautions
- Cardiovascular:
  - Underlying cardiovascular disease may be aggravated due to sexual activity or vasodilatory effects of tadalafil

- Patients with severely impaired autonomic control of blood pressure or left ventricular outflow obstruction (e.g., aortic stenosis, idiopathic hypertrophic subaortic stenosis) may have an increased sensitivity to vasodilators
- Not recommended in patients with veno-occlusive disease
- Not recommended in patients with angina occurring during sexual intercourse or unstable angina, uncontrolled arrhythmias, hypotension (less than 90/50 mmHg), uncontrolled hypertension, heart failure (NYHA Class 2 or greater) in the last 6 months, or myocardial infarction within the last 90 days

- Hematologic:
  - Patients with bleeding disorders or active peptic ulceration may experience increased bleeding times
- Hepatic:
  - Mild or moderate hepatic impairment (Child Pugh Class A or B); dose adjustment may be necessary
  - Severe hepatic impairment (Child Pugh Class C); avoid use
- Neurologic:
  - Not recommended for patients who experienced a stroke within the last 6 months
- Ophthalmic:
  - Sudden vision loss has been reported with phosphodiesterase type 5 (PDE5) inhibitors; drug discontinuation recommended
  - Not recommended in patients with hereditary degenerative retinal disorders, including retinitis pigmentosa
- Otic:
  - Sudden hearing decrease or loss has been reported; drug discontinuation recommended
- Renal:
  - Mild or moderate renal impairment (CrCl 31 and 80 mL/min); dose adjustment recommended
  - Severe renal impairment (CrCl less than 30 mL/min or on hemodialysis); avoid use
  - CrCl less than 50 mL/min or ESRD on hemodialysis; dose adjustment recommended for on-demand use
  - CrCl 30 to 50 mL/min; dose adjustment recommended for daily use
- Reproductive:
  - Priapism or prolonged erections lasting greater than 4 hours have been rarely reported; use caution in patients with conditions that predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia) or with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease)
- Concomitant Use:
  - Avoid use when initiating ritonavir
  - Avoid use with potent CYP3A inhibitors (e.g., itraconazole, ketoconazole) or potent CYP3A inducers (e.g., rifampin)
  - Use with other phosphodiesterase type 5 (PDE5) inhibitors or erectile dysfunction therapies not recommended
- Use with alpha blockers not recommended

Pregnancy and Lactation
Pregnancy Category B — not indicated for use in women.
Breast feeding – Infant risk cannot be ruled out

Interactions
Nitrates — Phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contraindicated in patients receiving such drugs. An interaction between tadalafil and sublingual glyceryl trinitrate was reported to occur when glyceryl trinitrate was given within 24 hours after tadalafil but was no longer detectable at 48 hours. Licensed product information recommends that if nitrate treatment is needed in a life-threatening situation then it should only be given at least 48 hours after the last dose of tadalafil and under close medical supervision.
Alpha-Blockers — Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, 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.
Antihypertensives — PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following co-administration of tadalafil with these agents compared with placebo.
Alcohol — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with tadalafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Adverse Drug Reaction
Common
- **Dermatologic:** Flushing (1% to 13%), hypersensitivity reactions, rash
- **Gastrointestinal:** Indigestion (1% to 13%), Nausea (up to 11%), dyspepsia, abdominal pain, vomiting, gastro-esophageal reflux
- **Musculoskeletal:** Backache (2.4% to 12%), Myalgia (1% to 14%)
- **Neurologic:** Headache (3% to 42%), dizziness
- **Respiratory:** Nasopharyngitis (2% to 13%), Respiratory tract infection (3% to 13%), nasal congestion, dyspnea, epistaxis

Serious
- **Cardiovascular:** Angina (less than 2%), Chest pain (less than 2%), Heart failure, Myocardial infarction (less than 2%), Tachycardia (less than 2%), palpitations, flushing, hypotension, hypertension, peripheral edema, fatigue
- **Dermatologic:** Stevens-Johnson syndrome
- **Neurologic:** Cerebral hemorrhage, Cerebrovascular accident, Seizure
- **Ophthalmic:** Anterior ischemic optic neuropathy, Non-arteritic, Retinal artery occlusion, Thrombosis of retinal vein, blurred vision, sensations described as eye pain
- **Otic:** Decreased hearing, Sudden onset (less than 2%), Sudden hearing loss (less than 2%), tinnitus
- Hematuria
- Prolonged erections

Overdose and Treatment
Single doses 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. Hemodialysis contributes negligibly to tadalafil elimination.

Storage Condition
Store at temperatures not exceeding 30°C.

Availability
Tadalafil (Caliberi) 5 mg orodispersible film: PET/Alu/Rayopeel® Laminate sachet x 1's (Box of 15's)
Tadalafil (Caliberi) 20 mg orodispersible film: PET/Alu/Rayopeel® Laminate sachet x 1's (Box of 2's and 15's)

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph". Seek medical attention immediately at the first sign of any adverse drug reaction.

Registration Numbers:
Tadalafil (Caliberi) 5 mg orodispersible film: DR-XY47290
Tadalafil (Caliberi) 20 mg orodispersible film: DR-XY47289

Date of First Authorization:
Tadalafil (Caliberi) 5 mg orodispersible film: 31 May 2021
Tadalafil (Caliberi) 20 mg orodispersible film: 31 May 2021

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Imported by:
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Metro Manila, Philippines

Date of Revision of Package Insert: June 2021
Martindale 36th Ed., 2009; PSUR March 2021

Abbott
PM042201