CALIBERI®
Tadalafil

1. NAME OF THE MEDICINAL PRODUCT
CALIBERI® 5 mg, 10 mg and 20 mg orodispersible films.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each orodispersible film contains 5 mg, 10 mg or 20 mg tadalafil.

Excipients: Each orodispersible film contains 0,2; 0,4 or 0,8 mg sucralose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Orodispersible film.
The 5 mg, 10 mg and 20 mg orodispersible films are light yellow orodispersible films.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Treatment of erectile dysfunction in adult men (ED).

4.2. Posology and method of administration
Method of administration:
CALIBERI® is available as 5 mg, 10 mg and 20 mg orodispersible films for oral use.

Posology:
Use in adult men
Erectile Dysfunction
The recommended dose is 10 mg taken prior to anticipated sexual activity and without regard to 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 dosing frequency is once per day.

Tadalafil 10 and 20 mg 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 of CALIBERI® (i.e., at least twice weekly) a once daily regimen with the lowest doses of CALIBERI® 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 appropriateness of continued use of the daily regimen should be reassessed periodically.

Use in elderly men
Dosage adjustments are not required in elderly patients.

Use in men with impaired renal function
Dosage 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. (See section 4.4 and 5.2 Pharmacokinetic properties).

Use in men with impaired hepatic function
The recommended dose of CALIBERI® is 10 mg taken prior to anticipated sexual activity and without regard to food. There is limited clinical data on the safety of CALIBERI® in patients with severe hepatic insufficiency (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 prescribing physician. (See section 5.2).

Use in men with diabetes
Dosage adjustments are not required in diabetic patients.

Paediatric population
CALIBERI® should not be used in individuals below 18 years of age.

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 CALIBERI® to patients who are using any form of organic nitrate is contraindicated. (See section 4.5).

Agents for the treatment of erectile dysfunction, including CALIBERI®, 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.

CALIBERI® is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4. Special warning and special precautions for use

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

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 (see section 5.1) and as such potentiate the hypotensive effect of nitrates (see section 4.3).

In patients receiving concomitant antihypertensive medicines, tadalafil may induce a bloodpressure decrease. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in occurred during clinical studies of CALIBERI® trials. In addition, hypertension and hypotension (including postural hypotension) were also seen infrequently in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to CALIBERI®, to sexual activity, or to a combination of these or other factors.

Visual defects and cases of NAION have been reported in connection with the intake of CALIBERI® and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CALIBERI® and consult a physician immediately (see section 4.3).

Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of CALIBERI® is not recommended in patients with severe renal impairment.

There is limited clinical data on the safety of single-dose administration of CALIBERI® in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day administration has not been evaluated in patients with hepatic insufficiency. If CALIBERI® is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Agents for the treatment of erectile dysfunction, including CALIBERI®, 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 anaemia, multiple myeloma or leukaemia).

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment. It is not known if CALIBERI® is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

In patients who are taking alpha 1 blockers concomitant administration of CALIBERI® may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

The combination of tadalafil and guanylate cyclase stimulators, is not recommended because it may lead to symptomatic hypotension.

Caution should be exercised when prescribing CALIBERI® to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicines are combined (see section 4.5).

The safety and efficacy of combinations of CALIBERI® and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take CALIBERI® with such combinations.

Hearing: Sudden decreased or loss of hearing, which may be accompanied by tinnitus, has been reported in association with the use of tadalafil. Physicians should advised patients to stop taking tadalafil and seek prompt medical attention in the event of sudden decreased or loss of hearing.

4.5. Interaction with other medicinal products and other forms of interaction

Interaction studies were conducted with 10 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.

Effects of other substances on tadalafil

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 (see section 4.4)
Consequently the incidence of the undesirable effects listed in section 4.8 might be increased.

The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. There is thus the potential of drug interactions mediated by inhibition of transporters.

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.

Effects of tadalafil on other medicinal products
In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of CALIBERI® to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical study in which 150 subjects receiving 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 CALIBERI® (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 CALIBERI® before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

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 (see section 4.4).

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 clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive agents was examined. Major classes of antihypertensive agents were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicines, 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 medicines. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicines.

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 medicines.
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 concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration 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 maximize 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).

An increase in gastric pH resulting from administration of nizatidine had no significant effect on tadalafil pharmacokinetics.

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.

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.

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.

Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Specific interaction studies with antidiabetic agents were not conducted.

4.6. Pregnancy and lactation

CALIBERI® is not indicated for use by women.

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 (see section 5.3). As a precautionary measure, it is preferable to avoid the use of CALIBERI® during pregnancy.

Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. CALIBERI® should not be used during breast feeding.

4.7. Effect on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. 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 CALIBERI®, before driving or operating machinery.

4.8. Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse reactions were headache and dyspepsia. The adverse reactions reported were transient, and generally mild or moderate. Adverse reactions data are limited in patients over 75 years of age.

b. Tabulated summary of adverse reactions

The table below lists the adverse reactions reported in erectile dysfunction placebo-controlled clinical trials in patients treated with CALIBERI® on demand and daily

dosing with doses within the currently approved dosing range for CALIBERI®. Adverse reactions are also included that have been reported from postmarketing surveillance in patients taking CALIBERI®.

Adverse reactions

Frequency estimate: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000) and Not known (events not reported in registration trials cannot be estimated from postmarketing spontaneous reports).

Very common (≥1/10)	**Common** (≥1/100 to >1/10)	**Uncommon** (≥1/1000 to >1/100)	**Rare** (≥1/10,000 to > 1/1000)
Immune system disorders			
		Hypersensitivity reactions	
Nervous System disorders			
Headache	Dizziness		Stroke[1](including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[3], Seizures, Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION)[3], Retinal vascular occlusion[3]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss[2]
Renal and urinary disorders			
		Haematuria	
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[3], Ventricular arrhythmia[3]
Vascular disorders			

	Flushing	Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion		Epistaxis, Dyspnoea
Gastrointestinal disorders			
	Dyspepsia, diarrhoea in elderly patients (≥ 65), nausea	Abdominal pain, Gastro-oesophageal reflux, vomiting	
Skin and subcutaneous tissue disorders			
		Rash, Hyperhydrosis (sweating)	Urticaria, Stevens-Johnson syndrome[3], Exfoliative dermatitis[3]
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia		
Reproductive system and breast disorders			
		Penile haemorrhage, haematospermia	Prolonged erections, Priapism[3]
General disorders and administration site conditions			
	Fatigue	Chest pain[1], peripheral oedema	Facial oedema[3], Sudden cardiac death[1,3]

(1) Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors (See section 4.4).
(2) Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil.
(3) Post marketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials

4.9. Overdose

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, ATC Code G04BE08.

Mechanism of action in ED 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 cavemosum. 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.

Pharmacodynamic effects

Studies in vitro have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavemosum 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 > 10,000-fold 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 > 10,000-fold 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 and 14-fold more potent for PDE5 than for PDE 11. The tissue distribution and physiological effects of the inhibition of PDE8 through PDE11 have not been elucidated.

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 CALIBERI® 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 l, 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 1/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).

Linearity/non-linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

Special Populations
Elderly
Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal insufficiency
In clinical pharmacology studies using single-dose tadalafil (5-20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, Cmax was 41% higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of CALIBERI® in patients with severe hepatic insufficiency (Child-Pugh Class C). There are no available data about the administration of once-a-day dosing of tadalafil to patients with hepatic impairment. If CALIBERI® is prescribed once-a-day, 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.

Patients with diabetes
Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

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. In a rat pre- 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. See also sections 4.4 Special warnings and special precautions for use and 5.1.

6. PHARMACEUTICAL PARTICULARS
6.1. List of Excipients
Orodispersible film:
Hydroxypropyl cellulose, xanthan gum, glycerin, polyethylene glycol 400, mannitol, simethicone emulsion (30%), titanium dioxide, polysorbate 80, sucralose, ferric oxide-yellow, ferric oxide-red, vanilla flavor.

6.2. Incompatibilities
Not applicable**.**

6.3. Shelf life
5, 10 mg and 20 mg: 3 years

6.4. Special precautions for storage
Store below 30°C. Store in the original package.

6.5. Instructions for use and handling
No special requirements.

6.6. Presentation
CALIBERI® 5 mg, box of 2 sachets@ 1 orodispersible film
Reg. No. DKI1950700396A1
CALIBERI® 5 mg, box of 4 sachets @ 1 orodispersible film
Reg. No. DKI1950700396A1
CALIBERI® 5 mg, box of 15 sachets @ 1 orodispersible film
Reg. No. DKI1950700396A1
CALIBERI® 10 mg, box of 2 sachets @ 1 orodispersible film
Reg. No. DKI1950700396B1
CALIBERI® 10 mg, box of 4 sachets @ 1 orodispersible film
Reg. No. DKI1950700396B1
CALIBERI® 10 mg, box of 15 sachets @ 1 orodispersible film
Reg. No. DKI1950700396B1
CALIBERI® 20 mg, box of 2 sachets @ 1 orodispersible film
Reg. No. DKI1950700396C1
CALIBERI® 20 mg, box of 4 sachets @ 1 orodispersible film
Reg. No. DKI1950700396C1
CALIBERI® 20 mg, box of 15 sachets @ 1 orodispersible film
Reg. No. DKI1950700396C1

HARUS DENGAN RESEP DOKTER

Manufactured by:
CTCBio Inc., Republic of Korea

Imported by:
PT. Abbott Indonesia
Jl. Raya Jakarta-Bogor KM. 37
Cimanggis, Depok
Indonesia

A023/06/19

INFORMASI PRODUK UNTUK PASIEN

CALIBERI® 5 mg, 10 mg, dan 20 mg
Orodispersible film
Tadalafil

Bacalah seluruh leaflet ini dengan saksama sebelum anda memulai penggunaan obat ini.

- Simpanlah leaflet ini di tempat yang aman, agar dapat dibaca kembali jika diperlukan.
- Jika ada pertanyaan lebih lanjut, hubungilah dokter atau apoteker.
- Obat ini diresepkan untuk Anda. Jangan diberikan kepada orang lain. Hal tersebut dikarenakan obat ini dapat saja membahayakan orang lain, walaupun gejala yang dialami sama dengan Anda.
- Jika mengalami efek samping, hubungilah dokter atau apoteker, termasuk kemungkinan efek samping yang tidak tercantum pada leaflet ini.

Pada leaflet ini terdapat informasi berikut:

1. APAKAH CALIBERI® DAN KEGUNAANNYA?

CALIBERI® mengandung zat aktif Tadalafil yag tergabung dalam kelompok obat-obatan bernama inhibitor fosfodiesterase tipe 5.

CALIBERI® digunakan dalam pengobatan pada pria dewasa sebagai berikut:

- Disfungsi ereksi. Kondisi ini adalah ketika seorang lelaki tidak dapat mencapai atau mempertahankan ereksi dan penis yang keras untuk melakukan kegiatan seksual. CALIBERI® telah terbukti secara dignifikan meningkatkan kemampuan penis untuk mencapai ereksi dan mempertahankan kekerasannya guna melakukan kegiatan seksual. Dengan adanya rangsangan seksual CALIBERI® bekerja dengan membantu pembuluh darah pada penis menjadi kendur sehingga darah mengalir ke dalam penis. Hasilnya adalah peningkatan fungsi ereksi. CALIBERI® tidak akan membantu jika tidak terdapat disfungsi ereksi.

  Penting untuk diperhatikan bahwa CALIBERI® tidak dapat bekerja jika tidak ada rangsangan seksual. Anda dan pasanga Anda perlu untuk saling memberikan rangsangan seperti halnya ketika tidak menggunakan obat untuk disfungsi ereksi.

2. APAKAH HAL YANG HARUS DIPERHATIKAN SEBELUM MENGGUNAKAN CALIBERI®?

JANGAN MEMINUM CALIBERI®:

- Jika memiliki alergi terhadap Tadalafil atau komposisi lain dari obat ini (terdapat pada poin nomor 6).

DISETUJUI OLEH BPOM : 08/08/2024

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- Jika sedang mengkonsumsi segala jenis donor nitrat organik atau nitrat oksida seperti Amyl nitrat. Ini merupakan golongan obat ("nitrat") yang digunakan untuk pengobatan angina pectoris ("nyeri dada"). CALIBERI® telah terbukti meningkatkan efek dari obat-obatan tersebut. jika sedang mengkonsumsi segala jenis nitrat atau Anda ragu, sampaikan kepada dokter.
- Jika memiliki penyakit jantung serius atau baru saja mengalami serangan jantung dalam jangka waktu 90 hari terakhir.
- Jika baru saja mengalami stroke dalam jangka waktu 6 bulan.
- Jika memiliki tekanan darah rendah atau tekanan darah tinggi yang tidak terkontrol.
- Jika pernah mengalami kehilangan penglihatan dikarenakan *non-arteritic ischemic optic neuropathy* (NANION), sebuah kondisi yang disebut sebagai stroke mata.

Peringatan dan Perhatian
Hubungi dokter sebelum memulai penggunaan CALIBERI®.

Waspadalah bahwa kegiatan seksual dapat mendatangkan resiko kepada pasien sakit jantung karena hal tersebut memberikan tekanan berlebih ke jantung. Jika memiliki masalah jantung, sampaikan kepada dokter.

Sebelum mengkonsumsi CALIBERI®, sampaikan kepada dokter jika memiliki:
- *Sickle cell anaemia* (ketidaknormalan sel darah merah).
- *Multiple myeloma* (kanker sumsum tulang).
- *Leukemia* (kanker sel darah).
- Segala bentuk deformation penis).
- Masalah penyakit pada hati yang serius.
- Masalah ginjal yang serius.

Belum diketahui apakah CALIBERI® efektif pada pasien yang pernah mengalami:
- Operasi panggul.
- Pengangkatan sebagian atau seluruh bagian kelenjar prostat dimana saraf prostat dipotong (*radical non-serve-sparing prostatectomy*).

Jika mengalami penurunan atau kehilangan penglihatan secara mendadak, hentikan penggunaan CALIBERI® dan segera hubungi dokter.

CALIBERI® tidak diperuntukkan bagi perempuan.

Anak-anak dan remaja
CALIBERI® tidak diperuntukkan bagi anak-anak dan remaja di bawah usia 18 tahun.

Penggunaan Obat Lain Bersama CALIBERI®
Sampaikan kepada dokter jika sedang atau baru saja atau mungkin akan mengkonsumsi obat-obat lainnya.

Jangan minum CALIBERI® jika sedang mengkonsumsi obat golongan nitrat.

Beberapa obat-obatan dapat dipengaruhi efeknya oleh CALIBERI® atau sebaliknya obat tersebut dapat mempengaruhi efek kerja CALIBERI®. Sampaikan kepada dokter atau apoteker jika sedang mengkonsumsi obat berikut:

- *Alpha blocker* (obat yang digunakan untuk mengobati tekanan darah tinggi atau gejala gangguan kencing yang terkait dengan sakit *benign prostatic hyperplasia*).
- Obat-obatan lain untuk mengobati tekanan darah tinggi.
- 5-*alpha reductase inhibitor(*obat yang digunakan untuk mengobati benign prostatic *hyperplasia*).
- Obat-obatan seperti ketokonazol (untuk mengobati infeksi jamur) dan *protease inhibitor* untuk mengobati infeksi AIDS atau HIV.
- Fenobarbital, fenitoin dan karbamazepin (obat-obatan antikonvulsan).
- Rifampisin, eritromisin, klaritomisin atau itrakonazol.
- Obat disfungsi ereksi lainnya.

Penggunaan CALIBERI® dengan minuman dan alkohol
lnformasi mengenai efek alkohol ada pada bagian 3. Jus *grapefruit* dapat mempengaruhi seberapa bagus efek CALIBERI® dan sebaiknya diminum dengan hati-hati. Konsultasikan kepada dokter untuk informasi lebih lanjut.

Kesuburan
Terdapat penurunan pematangan sperma di dalam testis ketika CALIBERI® diberikan ke anjing. Penurunan sperma ini nampak juga di beberapa orang. Efek tersebut mengarah kepada penurunan kesuburan.

Mengendarai dan Mengoperasikan Mesin
Beberapa orang yang mengkonsumsi CALIBERI® pada saat uji klinik melaporkan adanya kejadian pening. Periksa dengan saksama bagaimana reaksi tubuh Anda terhadap obat ini sebelum mengendarai atau mengoperasikan mesin.

3. BAGAIMANA CARA MEMINUM CALIBERI®?

Selalu minum obat ini seperti yang dokter perintahkan. Hubungi dokter atau apoteker jika ada keraguan.

Orodispersible film CALIBERI® hanya untuk diminum oleh lelaki. Telan satu orodispersible film utuh dengan air. Orodispersible film ini dapat diminum dengan atau tanpa makan terlebih dahulu.

Mengkonsumsi minuman beralkohol dapat mempengaruhi kemampuan mencapai ereksi dan dapat menurunkan tekanan darah untuk sementara waktu. Jika Anda telah atau berencana untuk meminum CALIBERI®, hindari minum minuman beralkohol secara berlebihan (kadar alkohol dalam darah mencapai 0.08% atau lebih), karena hal tersebut dapat meningkatkan resiko pening ketika berdiri.

Untuk pengobatan disfungsi ereksi

- Penggunaan sebelum hubungan seksual: dosis awal yang direkomendasikan adalah orodispersible film 10 mg sebelum melakukan hubungan seksual. Jika efek dari dosis ini

terlalu lemah, Dokter dapat menaikkan dosis menjadi 20 mg.Orodispersible film CALIBERI® diperuntukkan untuk penggunaan oral. Anda dapat meminum orodispersible film CALIBERI® 30 menit sebelum melakukan hubungan seksual. CALIBERI® masih dapat efektif hingga 36 jam setelah diminum. Jangan meminum CALIBERI® lebih dari sekali dalam sehari. CALIBERI®10 mg dan 20 mg ditujukan untuk digunakan sebelum melakukan hubungan seksual dan tidak direkomendasikan untuk penggunaan harian bersinambungan.

- Penggunaan sekali sehari (*once a day*): Dosis yang direkomendasikan adalah orodispersible film 5 mg diminum sekali sehari pada waktu yang kira-kira sama setiap harinya. Jangan minum CALIBERI® lebih dari sekali dalam sehari.
  CALIBERI® dosis sekali sehari (once a day) dapat berguna bagi lelaki yang menginginkan aktifitas seksual dua kali atau lebih dalam seminggu.
  Ketika mengkonsumsi CALIBERI® *once a day* ereksi dapat terjadi setiap saat dalam kurun waktu 24 jam, ketika ada rangsangan seksual.

Perlu diingat bahwa CALIBERI® tidak dapat bekerja jika tidak ada rangsangan seksual. Anda dan partner Anda perlu untuk saling memberikan rangsangan, seperti halnya ketika tidak mengkonsumsi obat untuk disfungsi ereksi.

Konsumsi alkohol dapat mempengaruhi kemampuan Anda untuk ereksi.

Jika Meminum CALIBERI® Melebihi Seharusnya
Hubungi dokter. Anda mungkin akan mengalami kejadian efek samping seperti yang tertera pada bagian 4.

Jika Lupa Meminum CALIBERI®
Minum CALIBERI® segera setelah mengingat namun jangan meminum dosis ganda untuk menggantikan dosis yang terlupakan. Anda tidak boleh meminum CALIBERI® lebih dari sekali dalam sehari.

4. APAKAH KEMUNGKINAN EFEK SAMPING YANG TERJADI?

Seperti semua obat-obatan lainnya, CALIBERI® dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya. Efek-efek tersebut biasanya berupa ringan hingga sedang.
Jika mengalami efek samping berikut hentikan penggunaan obat ini dan segeralah minta bantuan medis:

- Reaksi alergi termasuk gatal-gatal kemerahan (frekuensi: tidak biasa terjadi).
- Nyeri dada - jangan gunakan nitrat, namun dapatkanlah bantuan medis dengan segera (frekuensi: tidak biasa terjadi).
- Ereksi yang terlalu lama dan mungkin menyakitkan setelah mengkonsumsi CALIBERI® (frekuensi: jarang). Jika mengalami ereksi yang seperti itu, yang berlangsung lebih dari 4 jam, segera hubungi dokter.
- Kehilangan penglihatan secara mendadak (frekuensi: jarang).
- Hilangnya pendengaran secara mendadak yang disertai dengan telinga berdenging

Efek samping lain yang dilaporkan:
Biasa Terjadi (terjadi pada 1 - 10 pasien dari 100)

- Sakit kepala, nyeri punggung, sakit otot, nyeri di lengan dan kaki, muka memerah, sesak napas, gangguan pencemaan, *reflux,* mual dan merasa lelah.

Tidak Biasa Terjadi (terjadi pada 1-10 pasien dari1.000)

- Pusing, sakit perut, muntah, pandangan buram, sakit mata, peningkatan keringat, susah bemapas, pendarahan dari atau pada penis, timbulnya darah pada cairan mani, timbulnya darah pada urin, sensasi jantung berdebar-debar, detak jantung yang cepat, tekanan darah tinggi, tekanan darah rendah, hidung berdarah, telinga berdenging, tangan, telapak atau pergelangan kaki yang membengkak.

Jarang Terjadi (terjadi pada 1-10 pasien dari 10.000)

- Pingsan, kejang dan kehilangan ingatan. kelopak mata membengkak, mata merah, penurunan atau kehilangan pendengaran dan gatal-gatal (bilur merah gatal pada permukaan kulit).

Serangan jantung dan stroke pemah juga dilaporkan dengan frekuensi jarang. Sebagian besar dari pelapor telah diketahui memiliki masalah jantung sebelum mengkonsumsi CALIBERI®.

Penurunan daya atau kehilangan penglihatan pada satu mata atau keduanya baik secara sebagian, sementara atau permanen juga pernah dilaporkan dengan frekuensi jarang.
Beberapa tambahan efek samping yang jarang terjadi pada lelaki yang mengkonsumsi CALIBERI® yang tidak ditemui pada saat uji klinik. Efek tersebut meliputi:

- Migren, pembengkakan muka, reaksi alergi yang serius yang menyebabkan pembengkakan wajah atau tenggorokan, ruam kulit yang serius, beberapa gangguan yang mempengaruhi aliran darah ke mata, detak jantung yang tidak teratur, angina dan kematian mendadak karena gagaI jantung.

Efek samping berupa pening dan diare dilaporkan terjadi lebih sering pada lelaki berusia lebih dari 75 tahun yang mengkonsumsi CALIBERI®. Diare dilaporkan terjadi lebih sering pada lelaki berusia lebih dari 65 tahun yang mengkonsumsi CALIBERI®.

Jika mengalami efek samping apa pun, sampaikan kepada dokter atau apoteker. Termasuk jika mengalami efek samping yang mungkin terjadiyang tidak tercantum pada leaflet ini.

5. BAGAIMANA CARA MENYIMPAN CALIBERI®?

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini melebihi waktu kadaluwarsa yang tercantum pada kemasan karton dan blister berupa tulisan "EXP". Tanggal kadaluwarsa tersebut merujuk pada tanggal terakhir dari bulan berjalan.

Simpan di dalam kemasan aslinya untuk melindungi dari kelembaban. Jangan simpan di atas suhu 30°C.

Jangan buang obat apapun melalui saluran pembuangan air limbah rumah tangga. Tanyakan kepada apoteker bagaimana cara membuang obat jika sudah tidak lagi digunakan. Perilaku ini akan membantu perlindungan lingkungan.

DISETUJUI OLEH BPOM : 08/08/2024

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6. BAGAIMANA ISI KEMASAN DAN APAKAH INFORMASI PENTING LAINNYA?

Apakah kandungan CALIBERI®?

- Zat aktif CALIBERI® adalah tadalafil. Setiap orodispersible film mengandung 5 mg. 10 mg dan 20 mg tadalafil.
- Komposisi lainnya adalah:
  Hydroxypropyl cellulose, xanthan gum, glycerin, polyethylene glycol 400, mannitol, simethicone emulsion (30%), titanium dioxide, polysorbate 80, sucralose, ferric oxide-yellow, ferric oxide-red, vanilla flavor.

Seperti apakah wujud CALIBERI® dan isi kemasannya

CALIBERI® 5 mg, 10 mg dan 20 mg berupa orodispersible film berwarna kuning muda.

Besar kemasan dan Nomor registrasi

CALIBERI® 5 mg tersedia dalam kemasan 2 sachet, 4 sachet dan 15 sachet masing-masing berisi 1 orodispersible film yang terkemas dalam karton.
Nomor registrasi berturut-turut:
DKI1950700396A1; DKI1950700396A1; DKI1950700396A1

CALIBERI® 10 mg tersedia dalam kemasan 2 sachet, 4 sachet dan 15 sachet masing-masing berisi 1 orodispersible film yang terkemas dalam karton.
Nomor registrasi berturut-turut:
DKI1950700396B1; DKI1950700396B1; DKI1950700396B1

CALIBERI® 20 mg tersedia dalam kemasan 2 sachet, 4 sachet dan 15 sachet masing-masing berisi 1 orodispersible film yang terkemas dalam karton.
Nomor registrasi berturut-turut:
DKI1950700396C1; DKI1950700396C1; DKI1950700396C1

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
CTCBio Inc., Republic of Korea

Diimpor oleh:
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A023/06/19