Summary of Product Characteristics Cosagra Film Coated Tablets 50mg (Sildenafil Tablets 50mg)

1. **Name of the Medicinal Product**
   Cosagra Film Coated Tablets

2. **Qualitative and Quantitative Composition**
   Each Film coated tablet contains 50 mg of sildenafil (as citrate)

3. **Pharmaceutical Form**
   Film Coated Tablet

4. **Clinical Particulars**

4.1 Therapeutic Indications

Treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.
In order for Sildenafil to be effective, sexual stimulation is required.

4.2 Posology and Method of administration

Posology

Use in adults
The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and tolerability, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. If Sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state.

Elderly patients
Dosage adjustments are not required in elderly patients (≥ 65 years old).

Paediatric population
Sildenafil is not indicated for individuals below 18 years of age.

Method of administration
For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 7.1.
Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, sildenafil was shown to potentiate the

hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

4.4 Special warnings and 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.

Cardiovascular risk factors

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.

Priapism

Agents for the treatment of erectile dysfunction, including sildenafil, 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).

Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction. Therefore the use of such combinations is not recommended.

Effects on vision

Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE_5 inhibitors. Patients should be advised that in the event of any sudden visual defect, they should stop taking Sildenafil and consult a physician immediately.

Effect on bleeding
There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered to these patients only after careful benefit-risk assessment.

Women
Sildenafil is not indicated for use by women.

4.5 Interaction with other medicinal products and other forms of interaction

Sildenafil can cause a serious drop in your blood pressure when used with nitrates, which can lead to dizziness, fainting, and rarely heart attack or stroke. Do not use sildenafil with any of the following: certain drugs used to treat chest pain/angina (nitrates such as nitroglycerin, isosorbide), recreational drugs called "poppers" containing amyl or butyl nitrite. If you are also taking an alpha blocker medication (such as doxazosin, tamsulosin) to treat an enlarged prostate/BPH or high blood pressure, your blood pressure may get too low which can lead to dizziness or fainting. Your doctor may start treatment with a lower dose of sildenafil to minimize your risk of low blood pressure. Other medications can affect the removal of sildenafil from your body, which may affect how sildenafil works. Examples include azole antifungals (such as itraconazole, ketoconazole), macrolide antibiotics (such as clarithromycin, erythromycin), HIV protease inhibitors (such as ritonavir, saquinavir), hepatitis C virus protease inhibitors (such as boceprevir, telaprevir), rifampin, among others. Do not take this medication with any other product that contains sildenafil or other similar medications for erectile dysfunction-ED or pulmonary hypertension (such as tadalafil, vardenafil)

4.6 Pregnancy and lactation

Sildenafil is not indicated for use by women.
There are no adequate and well-controlled studies in pregnant or breastfeeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to Sildenafil before driving or operating machinery.

4.8 Undesirable Effects

Summary of the safety profile

The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, visual disorders, nasal congestion, dizziness and visual colour distortion.

Adverse reactions from post-marketing surveillance has been gathered covering an estimated period >9 years. Because not all adverse reactions are reported to

the Marketing Authorisation Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

Tabulated list of adverse reactions

In the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency (very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000). In addition, the frequency of medically important adverse reactions reported from post-marketing experience is included as not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies and medically important adverse reactions reported through post-marketing surveillance

SYSTEM ORGAN CLASS	ADVERSE REACTIONS
Immune system disorders	
Rare	Hypersensitivity reactions
Nervous system disorders	
Very common	Headache
Common	Dizziness
Uncommon	Somnolence, Hypoaesthesia
Rare	Cerebrovascular accident, Syncope
Not known	Transient ischaemic attack, Seizure, Seizure recurrence
Eye disorders	
Common	Visual disorders, Visual colour distortion
Uncommon	Conjunctival disorders, Eye Disorders, Lacrimation Disorders, Other Eye Disorders
Not known	Non-arteritic anterior ischaemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect
Ear and labyrinth disorders	
Uncommon	Vertigo, Tinnitus
Rare	Deafness
Cardiac disorders	
Uncommon	Palpitations, Tachycardia
Rare	Myocardial infarction, Atrial fibrillation

Not known	Ventricular arrhythmia, Unstable angina, Sudden cardiac death
Vascular disorders	
Common	Flushing
Rare	Hypertension, Hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Nasal congestion
Rare	Epistaxis
Gastrointestinal disorders	
Common	Dyspepsia
Uncommon	Vomiting, Nausea, Dry mouth
Skin and subcutaneous tissue disorders	
Uncommon	Skin rash
Not known	Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Renal and urinary disorders	
Uncommon	Haematuria
Reproductive system and breast disorders	
Uncommon	Haematospermia, Penile haemorrhage
Not known	Priapism, Prolonged erection
General disorders and administration site conditions	
Uncommon	Chest pain, Fatigue
Investigations	
Uncommon	Heart rate increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

5 Overdose

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

6 Pharmacological Properties

6.1 Pharmacodynamic Properties

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

6.2 Pharmacokinetic Properties

Absorption

Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 41% (range 25-63%). After oral dosing of sildenafil AUC and Cmax increase in proportion with dose over the recommended dose range (25-100 mg).
When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in tmax of 60 minutes and a mean reduction in Cmax of 29%.

Distribution

The mean steady state volume of distribution (Vd) for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/mL (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the

mean maximum free plasma concentration for sildenafil of 18 ng/mL (38 nM). Protein binding is independent of total drug concentrations.

Biotransformation

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% that of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 h.

Elimination

The total body clearance of sildenafil is 41 l/h with a resultant terminal phase half-life of 3-5 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose).

6.3 Preclinical safety data

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

7 Pharmaceutical Particulars

7.1 List of Excipients

Microcrystalline Cellulose BP
Dicalcium Hydrogen Phosphate BP
Croscarmellose Sodium BP
Colloidal Anhydrous Silica BP
Magnesium Stearate BP
Opadry II Blue

7.2 Incompatibilities

None

7.3 Shelf life

2 Years

7.4 Special precautions for storage
Store in a dry place below 30°C. Protect from light.

7.5 Nature and contents of container
PVDC coated PVC/ALU blister packing

7.6 Instructions for use, handling and disposal
No special requirements

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11 Dosimetry (if applicable)
New registration

12 Instructions for Preparation of radiopharmaceuticals (if applicable)
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