

**Professional Information for ZYFORMA 25 / 50 / 100****SCHEDULING STATUS:** S4**1. NAME OF THE MEDICINE****ZYFORMA 25** film-coated tablets**ZYFORMA 50** film-coated tablets**ZYFORMA 100** film-coated tablets**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

ZYFORMA 25: Each film-coated tablet contains sildenafil citrate equivalent to 25 mg sildenafil.

ZYFORMA 50: Each film-coated tablet contains sildenafil citrate equivalent to 50 mg sildenafil.

ZYFORMA 100: Each film-coated tablet contains sildenafil citrate equivalent to 100 mg sildenafil.

*Excipients with known effect:*

Contains sugar.

ZYFORMA 25: Each tablet contains 2,1 mg lactose monohydrate.

ZYFORMA 50: Each tablet contains 4,2 mg lactose monohydrate.

ZYFORMA 100: Each tablet contains 8,4 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Film-coated tablets.

ZYFORMA 25: Light blue to blue, oval shaped, biconvex, film-coated tablets, plain on both sides.

ZYFORMA 50: Light blue to blue, oval shaped, biconvex, film-coated tablets, engraved 50 on one side and plain on other side.

ZYFORMA 100: Light blue to blue, oval shaped, bevelled, film-coated tablets, engraved 100 on

one side and plain on other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

ZYFORMA is indicated only for the treatment of erectile dysfunction.

THIS PRODUCT IS NOT AN APHRODISIAC.

### **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 toleration, the dose may be increased to 100 mg or decreased to 25 mg.

The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day.

The following factors are associated with increased plasma levels of ZYFORMA:

Age > 65 (40 % increase in AUC), hepatic impairment (e.g. cirrhosis, 80 %), severe renal impairment (creatinine clearance < 30 mL/min, 100 %), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin 182 %, saquinavir 210 %, ketoconazole, itraconazole 200 %, ritonavir 1 000 %).

#### **Special populations**

##### ***Use in patients with mild to moderately impaired renal function***

A starting dose of 25 mg should not be exceeded.

##### ***Use in patients with mild to moderately impaired hepatic function***

Since ZYFORMA clearance is reduced in patients with hepatic impairment (e.g. cirrhosis), a starting dose of 25 mg should not be exceeded.

***Use in elderly patients***

Healthy elderly volunteers (65 years or over) had a reduced clearance of ZYFORMA. A starting dose of 25 mg should be considered in patients older than 65 years of age.

***Use in patients using potent CYP 3A4 inhibitors***

Given the extent of the interaction with patients receiving concomitant therapy with cytochrome P450 3A4 inhibitors (e.g. ritonavir, erythromycin, saquinavir, ketoconazole, itraconazole), ZYFORMA should not be used concomitantly with these medicines (see section 4.3).

ZYFORMA was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated.

**Paediatric population**

ZYFORMA is not indicated for use in children.

**Method of administration**

ZYFORMA tablets are for oral administration.

**4.3 Contraindications**

- Hypersensitivity to sildenafil citrate or to any of the excipients listed in section 6.1.
- Consistent with its known effects on the nitric oxide/cGMP pathway (see section 5.1), ZYFORMA was shown to potentiate the hypotensive effects of acute and chronic nitrates, and its administration to patients who are concurrently using nitric oxide donors, organic nitrates or organic nitrites in any form either regularly or intermittently is therefore contraindicated.
- The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

- Concomitant use of ZYFORMA with potent cytochrome P450 3A4 inhibitors, e.g. ritonavir, erythromycin, saquinavir, ketoconazole and itraconazole is contraindicated.
- Medicines for the treatment of erectile dysfunction, including ZYFORMA, 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).
- ZYFORMA 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 (see section 4.4).
- The use of ZYFORMA is contraindicated in patients with severe hepatic impairment and patients with severe impairment of renal function (creatinine clearance < 30 mL/min) not on haemodialysis or continuous ambulatory peritoneal dialysis.
- The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: hypotension (blood pressure < 90/50 mm Hg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

#### 4.4 Special warnings and precautions for use

A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes, and identify appropriate treatment.

##### **Cardiovascular risk factors**

***There is a potential for cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatment for erectile dysfunction, including ZYFORMA should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.***

ZYFORMA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers. Medical practitioners should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g. aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

ZYFORMA potentiates the hypotensive effect of nitrates (see section 4.3).

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular dysrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of ZYFORMA. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of ZYFORMA without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

### ***Priapism***

Medicines for the treatment of erectile dysfunction, including ZYFORMA, 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).

Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

***Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction***

The safety and efficacy of combinations of sildenafil with other PDE5 inhibitors, or other pulmonary arterial hypertension (PAH) treatments containing sildenafil, or other treatments for erectile dysfunction have not been studied. 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 PDE5 inhibitors (see section 4.8). Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors (see section 4.8).

Patients should be advised that in the event of any sudden visual defect, they should stop taking ZYFORMA and consult a medical practitioner immediately (see section 4.3).

***Concomitant use with ritonavir***

Co-administration of ZYFORMA with ritonavir is contraindicated (see section 4.5).

***Concomitant use with alpha-blockers***

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in a few susceptible individuals (see section 4.5). This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered (see section 4.2). In addition, medical practitioners should advise patients what to do in the event of postural hypotensive symptoms.

***Effect on bleeding***

Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside *in vitro*. There is no safety information on the administration of sildenafil to

patients with bleeding disorders or active peptic ulceration. Therefore, ZYFORMA should be administered with caution to these patients.

### ***Hearing loss***

A sudden unilateral or bilateral decrease of loss of hearing (sensorineural deafness) with or without associated vestibular symptoms has been reported with the use of PDE5 inhibitors, including ZYFORMA. There is insufficient information regarding the reversibility of the hearing loss and the role of underlying risk factors for hearing loss in individual subjects.

### ***Women***

ZYFORMA is not indicated for use by women.

### ***ZYFORMA contains lactose monohydrate***

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ZYFORMA.

## **4.5 Interaction with other medicines and other forms of interaction**

### ***Effects of other medicines on ZYFORMA***

#### ***In vitro studies***

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

#### ***In vivo studies***

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25 mg

should be considered.

Co-administration of the human immunodeficiency virus (HIV) protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300 % (4-fold) increase in sildenafil  $C_{max}$  and a 1 000 % (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil has no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results, co-administration of sildenafil with ritonavir is contraindicated (see section 4.3).

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1 200 mg three times a day) with sildenafil (100 mg single dose) resulted in a 140 % increase in sildenafil  $C_{max}$  and a 210 % increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics (see section 4.2). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), there was a 182 % increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC,  $C_{max}$ ,  $t_{max}$ , elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite.

Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56 % increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest



increases in plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.

Although specific interaction studies were not conducted for all medicines, population pharmacokinetic analysis showed no effect of concomitant treatment on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

In a study of healthy male volunteers, co-administration of the endothelin antagonist, bosentan, (an inducer of CYP3A4 [moderate], CYP2C9 and possibly of CYP2C19) at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in 62,6 % and 55,4 % decrease in sildenafil AUC and  $C_{max}$ , respectively. Therefore, concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil.

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to result in a serious interaction with sildenafil.

### ***Effects of sildenafil on other medicines***

#### ***In vitro studies***

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 ( $IC_{50} > 150 \mu M$ ). Given sildenafil peak plasma concentrations of approximately 1  $\mu M$  after recommended doses, it is unlikely that ZYFORMA will alter the clearance of substrates of these

isoenzymes. There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

#### *In vivo studies*

Consistent with its known effects on the nitric oxide/cGMP pathway (see section 5.1), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated (see section 4.3).

Riociguat: Preclinical studies showed additive systemic blood pressure-lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated (see section 4.3).

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing (see sections 4.2 and 4.4). In three specific interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilised on doxazosin therapy.

In these study populations, mean additional reductions of supine blood pressure of 7/7 mm Hg, 9/5 mm Hg, and 8/4 mm Hg, and mean additional reductions of standing blood pressure of 6/6 mm Hg, 11/4 mm Hg, and 4/5 mm Hg, respectively, were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilised on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

No significant interactions were shown when sildenafil (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dL.

Pooling of the following classes of antihypertensive medication; diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicines (vasodilator and centrally acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment.

In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mm Hg. The corresponding additional reduction in supine diastolic blood pressure was 7 mm Hg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers.

Sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates. In healthy male volunteers, sildenafil at steady state (80 mg three times a day) resulted in a 49,8 % increase in bosentan AUC and a 42 % increase in bosentan  $C_{max}$  (125 mg twice a day).

#### **4.6 Fertility, pregnancy and lactation**

ZYFORMA is not indicated for use by women.

There are no adequate and well-controlled studies in pregnant or breastfeeding women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral

administration of sildenafil.

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

#### 4.7 Effects on ability to drive and use machines

ZYFORMA may have a minor influence on the ability to drive and use machines. As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to ZYFORMA, before driving or operating machinery.

#### 4.8 Undesirable effects

| MedDRA system organ class   | Frequency         | Adverse reactions                                                                                                                                                                                                                                                                               |
|-----------------------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Infections and infestations | Less frequent     | Rhinitis                                                                                                                                                                                                                                                                                        |
| Immune system disorders     | Less frequent     | Hypersensitivity                                                                                                                                                                                                                                                                                |
| Nervous system disorders    | Frequent          | Headache, dizziness                                                                                                                                                                                                                                                                             |
|                             | Less frequent     | Somnolence, hypaesthesia, cerebrovascular incident, transient ischaemic attack, syncope                                                                                                                                                                                                         |
|                             | Frequency unknown | Seizure, seizure recurrence                                                                                                                                                                                                                                                                     |
| Eye disorders               | Frequent          | Visual colour distortions, visual disturbance, blurred vision                                                                                                                                                                                                                                   |
|                             | Less frequent     | Lacrimation disorders, eye pain, photophobia, photopsia, ocular hyperaemia, visual brightness, conjunctivitis, retinal haemorrhage, arteriosclerotic retinopathy, retinal disorder, glaucoma, visual field defect, diplopia, visual acuity reduced, myopia, asthenopia, vitreous floaters, iris |

|                                                 |                   |                                                                                                                                                                                     |
|-------------------------------------------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                 |                   | disorder, mydriasis, halo vision, eye oedema, eye swelling, eye disorder, conjunctival hyperaemia, eye irritation, abnormal sensation in eye, eyelid oedema, scleral discolouration |
|                                                 | Frequency unknown | Non-arteritic anterior ischaemic optic neuropathy (NAION), retinal vascular occlusion                                                                                               |
| Ear and labyrinth disorders                     | Less frequent     | Vertigo, tinnitus, deafness                                                                                                                                                         |
| Cardiac disorders                               | Less frequent     | Tachycardia, palpitations, myocardial infarction, atrial fibrillation, unstable angina                                                                                              |
|                                                 | Frequency unknown | Sudden cardiac death, ventricular dysrhythmia                                                                                                                                       |
| Vascular disorders                              | Frequent          | Flushing, hot flush                                                                                                                                                                 |
|                                                 | Less frequent     | Hypertension, hypotension                                                                                                                                                           |
| Respiratory, thoracic and mediastinal disorders | Frequent          | Nasal congestion                                                                                                                                                                    |
|                                                 | Less frequent     | Epistaxis, sinus congestion, throat tightness, nasal oedema, nasal dryness                                                                                                          |
| Gastrointestinal disorders                      | Frequent          | Nausea, dyspepsia                                                                                                                                                                   |
|                                                 | Less frequent     | Gastro oesophageal reflux disease, vomiting, abdominal pain upper, dry mouth, oral hypaesthesia                                                                                     |
| Skin and subcutaneous tissue disorders          | Less frequent     | Rash                                                                                                                                                                                |
|                                                 | Frequency unknown | Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)                                                                                                                    |
| Musculoskeletal and connective                  | Less frequent     | Myalgia, pain in extremity                                                                                                                                                          |

|                                                      |                   |                                                        |
|------------------------------------------------------|-------------------|--------------------------------------------------------|
| tissue disorders                                     |                   |                                                        |
| Renal and urinary disorders                          | Less frequent     | Haematuria                                             |
| Reproductive system and breast disorders             | Less frequent     | Penile haemorrhage, haematospermia, increased erection |
|                                                      | Frequency unknown | Priapism                                               |
| General disorders and administration site conditions | Less frequent     | Chest pain, fatigue, feeling hot, irritability         |
| Investigations                                       | Less frequent     | Increased heart rate                                   |

### ***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of ZYFORMA is important. It allows continued monitoring of the benefit/risk balance of ZYFORMA. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

## **4.9 Overdose**

In single dose volunteer studies of doses up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200 mg did not result in increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was increased.

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Urologicals; Drugs used in erectile dysfunction.

ATC code: G04B E03.

Pharmacological classification: A 7.1.5 Vasodilators – peripheral.

Sildenafil restores impaired erectile function by increasing blood flow to the penis, in response to sexual stimulation.

Sildenafil is a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, during sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP, producing smooth muscle relaxation in the corpus cavernosum allowing the inflow of blood.

## **5.2 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 40 % (range 25 – 63 %). The oral pharmacokinetics of sildenafil is proportional over the recommended dose range (25 – 100 mg). When sildenafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in  $T_{max}$  of 60 minutes and a mean reduction in  $C_{max}$  of 29 %.

### ***Distribution***

The mean steady state volume of distribution ( $V_{ss}$ ) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating *N*-desmethyl metabolite are both approximately 96 % bound to plasma proteins. Protein binding is independent of total medicine concentrations. In healthy volunteers receiving sildenafil (100 mg single dose), less than 0,0002 % (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

**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 PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50 % that of the parent compound. 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 hours.

**Elimination**

The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3 – 5 hours. 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).

**Special patient groups***Elderly patients*

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40 % greater than those seen in healthy younger volunteers (18 – 45 years).

*Renal insufficiency*

In volunteers with mild (CL<sub>cr</sub> [creatinine clearance] = 50 – 80 mL/min) and moderate (CL<sub>cr</sub> = 30 – 49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered. In volunteers with severe (CL<sub>cr</sub> ≤ 30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100 %) and C<sub>max</sub> (88 %) compared to age-matched volunteers with no renal impairment.



### *Hepatic insufficiency*

In volunteers with hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84 %) and  $C_{max}$  (47 %) compared to age-matched volunteers with no hepatic impairment.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### ***Core tablet:***

Calcium hydrogen phosphate

Croscarmellose sodium

Hypromellose (E464)

Magnesium stearate (E572)

Microcrystalline cellulose (E460).

#### ***Film-coating:***

##### ***Opadry II Blue:***

FD&C Blue indigo carmine (colourant) (E132)

Hypromellose (E464)

Lactose monohydrate

Titanium dioxide (E171)

Triacetin.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years.

#### **6.4 Special precautions for storage**

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

#### **6.5 Nature and contents of container**

Clear PVC/PVDC/aluminium blister strips placed in an outer carton.

Aluminium/aluminium blister strips placed in an outer carton.

Pack size: 2 or 4 tablets.

#### **6.6 Special precautions for disposal and other handling**

No special requirements.

### **7. HOLDER OF CERTIFICATE OF REGISTRATION**

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

Tel: 012 748 6400

### **8. REGISTRATION NUMBERS**

ZYFORMA 25: 47/7.1.5/0676

ZYFORMA 50: 47/7.1.5/0677

ZYFORMA 100: 47/7.1.5/0678

### **9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

14 June 2022

**10. DATE OF REVISION OF THE TEXT**

06 November 2025