# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Sildazen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of suspension contains sildenafil citrate equivalent to 25 mg of sildenafil (35.1 mg as sildenafil citrate).
Each actuation delivers 0.5 mL of suspension which contains 12.5 mg of sildenafil.

Excipient with known effect:
Each millilitre of suspension contains 1 mg of sodium benzoate (E211).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

White to off-white suspension, free of foreign substances with mint odour.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Sildazen is indicated in adult men with erectile dysfunction.

In order for Sildazen to be effective, sexual stimulation is required.

### 4.2 Posology and method of administration

Posology

*Use in adults*
The recommended dose is 2 mL (4 actuations), equivalent to 50 mg of sildenafil taken as needed, approximately one hour before sexual activity. Based on efficacy and tolerability, the dose may be increased to 4 mL (8 actuations), equivalent to 100 mg, or decreased to 1 mL (2 actuations), equivalent to 25 mg of sildenafil. **The maximum recommended dose is 4 mL (8 actuations), equivalent to 100 mg of sildenafil.** The maximum recommended dosing frequency is once per day. If Sildazen is taken with food, the onset of its pharmacological activity may be delayed compared to the fasted state (see section 5.2).

| Number of actuations | Quantity of suspension delivered | Quantity of sildenafil |
|---|---|---|
| 2 | 1 mL | 25 mg |
| 4 | 2 mL | 50 mg |
| 8 | 4 mL | 100 mg |

Each actuation delivers 0.5 mL of product which contains 12.5 mg of sildenafil.

Special populations

*Elderly*
Dosage adjustments are not required in elderly patients (patients aged 65 years or older).

*Renal impairment*
The dosage recommendations described under “Use in adults” are applicable to patients with mild to moderate renal impairment (creatinine clearance = 30-80 mL/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 mL/min) a 25 mg dose (two actuations) should be considered for these patients. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg.

*Hepatic impairment*
Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose (two actuations) should be considered for these patients. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg.

*Paediatric population*
Sildazen is not indicated for children and adolescents below 18 years of age.

*Use in patients taking other medicinal products*
With the exception of ritonavir, for which co-administration with sildenafil is not advised (see section 4.4), a starting dose of 1 mL (2 actuations) equivalent to 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors (see section 4.5).

In order to minimise the potential for developing postural hypotension in patients receiving alpha-blocker treatment, patients should be stabilised on alpha-blocker therapy prior to initiating sildenafil administration. In addition, initiation of sildenafil treatment at a dose of 1 mL (2 actuations) equivalent to 25 mg should be considered (see sections 4.4 and 4.5).

Method of administration

For oral administration.

Not to be administered nasally or cutaneously (locally applied).

## INSTRUCTIONS FOR USE

1. Shake the bottle vigorously approximately 20 seconds to ensure that no drug precipitate is observed in the bottle before each use. See figure 1.

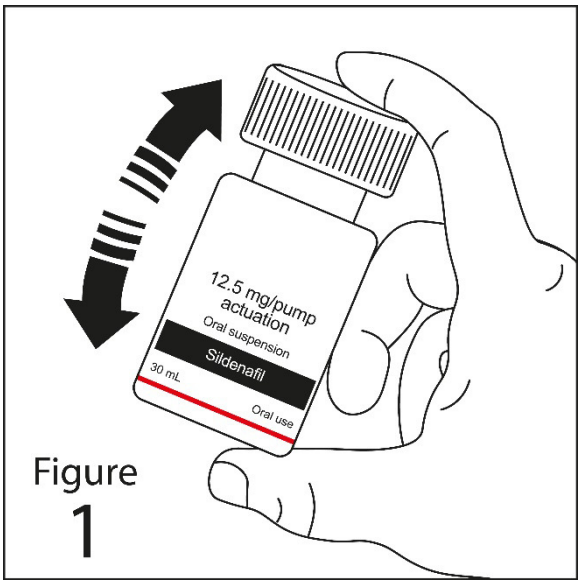


Figure 1

2. The child-resistant screw cap should be removed by pushing it down firmly and turning it anticlockwise. See figure 2.

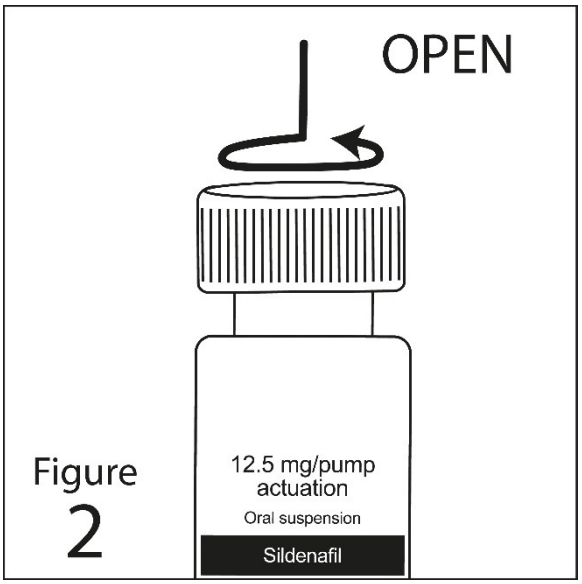


Figure 2

3. The dosage pump has to be placed on top of the bottle sliding the plastic tube carefully into the bottle. Then the dosing pump needs to be held onto the neck of the bottle and screwed clockwise until it is firmly attached. See figure 3.

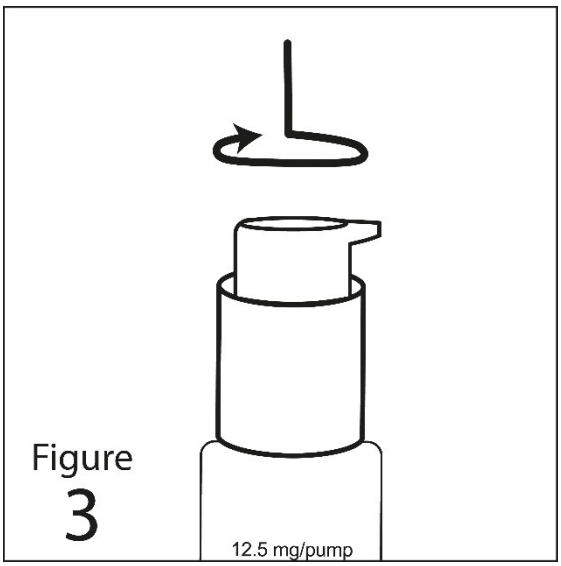


Figure 3

4. Twist the dosage pump into open position. See Figure 4.

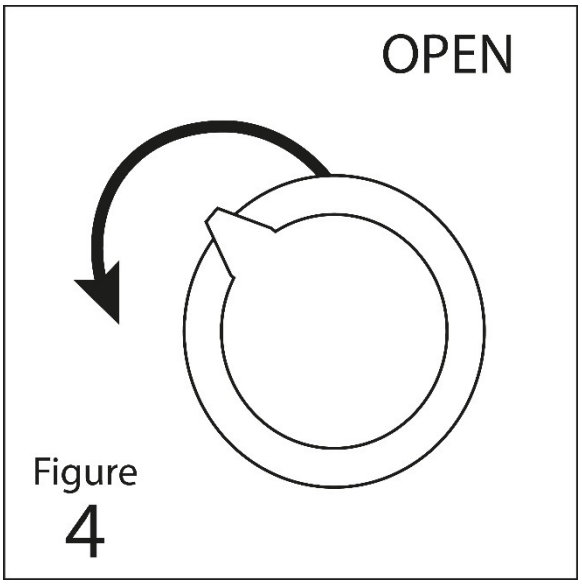


Figure 4

5. Before every use (including first-time use): Activate the pump three times to prepare (prime) the dosage pump, discard any product released during this activation into an absorbent material. The pump is now ready to be used and each metered spray delivers an average of 12.5 mg of sildenafil.
A failure in this priming process may lead to a lower dose when used.

**Discard the bottle when the drug level is below the red line.**

6. Tilt your head back a little. Place the pump in your mouth. Press the dosage pump as many times as required, according to the dose prescribed by your doctor and apply the suspension on the tongue and swallow the suspension immediately with saliva. Avoid direct contact between the end of the dosage pump and inside the mouth and tongue. See figure 5.

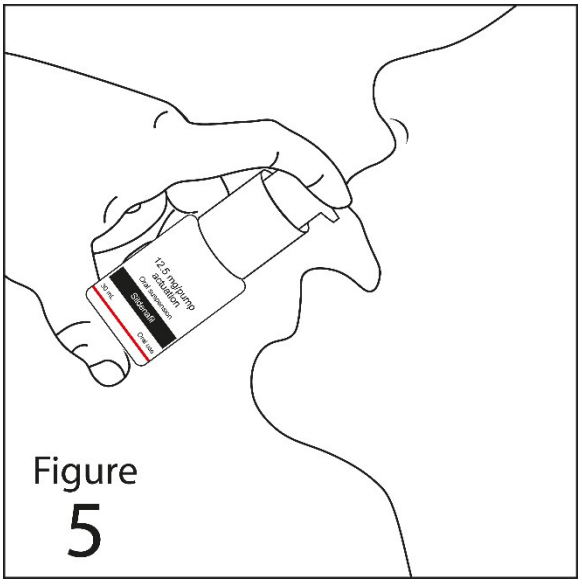
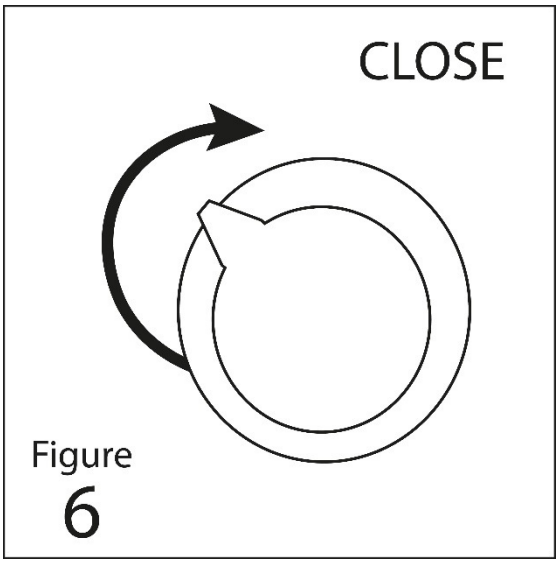
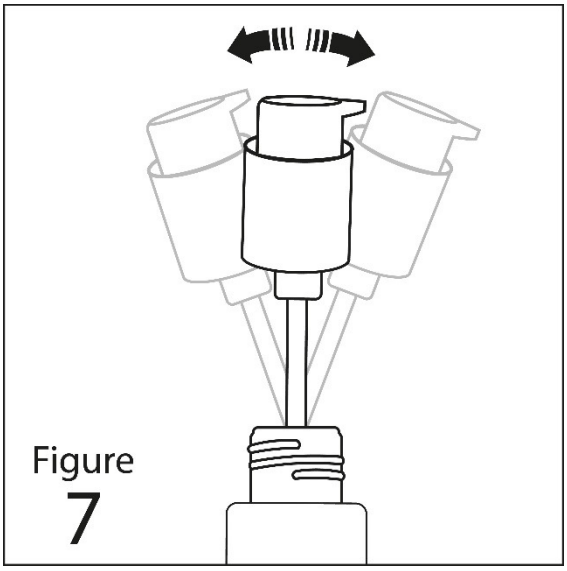


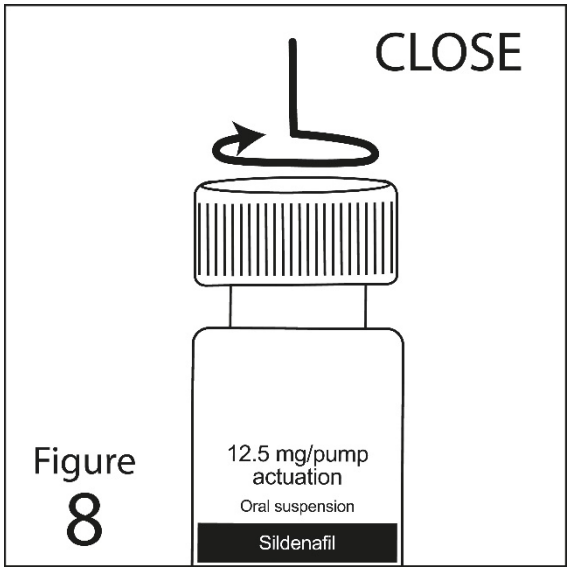
Figure 5

7. Twist the dosage pump to closed position (Figure 6) and remove the pump after dripping it against the internal walls of the bottle by unscrewing anticlockwise (Figure 7).

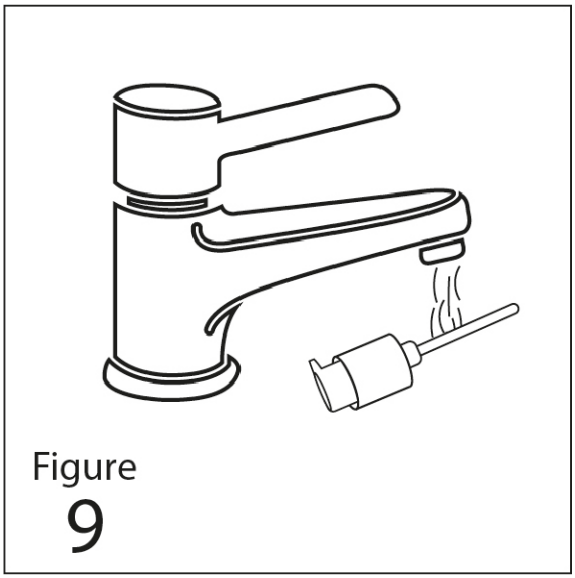


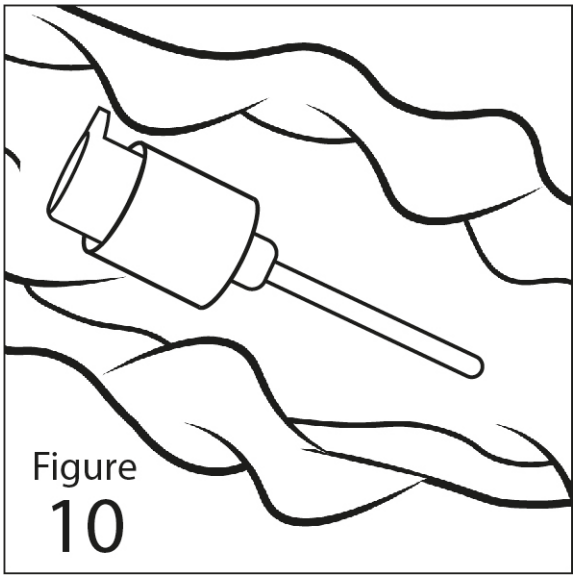




8. The child resistant screw cup should be put back on the bottle to close it immediately after each use (Figura 8).



9. Wash completely the dosage pump with water, ensuring no product or water remains in the pump by activating the pump several times into an absorbent material. Allow it to dry thoroughly before the next use. See figure 9 and figure 10.




Store this medicine out of the sight and reach of children.

NOTE FOR PATIENTS – With these instructions for use requiring repriming before each dose and washing the dosing pump, the bottle will contain a final average deliverable volume of 20 ml of the oral suspension.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway (see section 5.1), 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.

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).

Medicinal products 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 heart failure).

Sildenafil is contraindicated in patients who have loss of vision in one eye due to non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether or not this episode was associated with previous PDE5 inhibitor exposure (see section 4.4).

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated in these patients: severe hepatic impairment, hypotension (blood pressure <90/50 mmHg), 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 medical history and physical examination of the patient are advisable to diagnose erectile dysfunction and to determine potential underlying causes before considering pharmacological treatment.

For oral administration only. Not to be used by other routes of administration.

Cardiovascular risk factors
Prior to initiating any treatment for erectile dysfunction, the physician should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity.

Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Prior to prescribing sildenafil, the physician should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilator 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.

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

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing 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 sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

Priapism
Medicinal products 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 with 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, other pulmonary arterial hypertension (PAH) treatments containing sildenafil (REVATIO), 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 sildenafil and consult a physician immediately (see section 4.3).

Concomitant use with ritonavir
Co-administration of sildenafil with ritonavir is not advised (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 of both drugs may lead to symptomatic hypotension in a small number of more susceptible patients (see section 4.5). This is most likely to occur within 4 hours after taking sildenafil. In order to minimise the potential for developing postural hypotension, patients receiving alpha-blocker treatment should be haemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Furthermore, initiation of sildenafil treatment at a dose of 25 mg (two actuations) should be considered (see section 4.2). In addition, physicians should advise their patients what to do in the event of postural hypotensive symptoms.

Effects on bleeding
Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside *in vitro*. There are no safety data on the administration of sildenafil to patients with bleeding disorders or active peptic ulcer. Therefore, sildenafil should be administered to these patients only after benefit-risk assessment.

Use in women
Sildenafil is not indicated for use by women.

Warnings relating to excipients
This medicinal product contains 1 mg of sodium benzoate (E211) in each millilitre of suspension.

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

Effects of other medicinal products on sildenafil

*In vitro studies*
Sildenafil metabolism is mediated primarily by the cytochrome P450 (CYP) isoforms 3A4 (mostly) and 2C9 (to a lesser extent). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

*In vivo studies*
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 (two actuations) should be considered.

Co-administration of the HIV protease inhibitor ritonavir, which is a potent inhibitor of cytochrome P450, 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 large number of cytochrome P450 substrates. Sildenafil had no effect on the pharmacokinetics of ritonavir. Based on these pharmacokinetic results, co-administration of sildenafil with ritonavir is not advised (see section 4.4) and the maximum dose of sildenafil should under no circumstances exceed 25 mg (two actuations) in 48 hours.

Co-administration of the HIV protease inhibitor saquinavir, also a cytochrome 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 the pharmacokinetics of saquinavir (see section 4.2). Stronger cytochrome 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, there was a 182% increase in sildenafil systemic exposure (AUC) when a stable plasma concentration of erythromycin (500 mg twice daily for 5 days) was reached. In 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 cytochrome 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 have not been conducted for all medicinal products, pharmacokinetic data analysis showed no effect on the pharmacokinetics of sildenafil when co-administered with CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazides 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 with healthy male volunteers, co-administration of the endothelin antagonist, bosentan (an inducer of CYP3A4 [moderate], of CYP2C9 and possibly of CYP2C19), at steady state (125 mg twice daily) with sildenafil at steady state (80 mg three times daily) resulted in a 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 a potassium channel activator and nitrate. Due to its nitrate component, it has the potential to result in a serious interaction with sildenafil.

<u>Effects of sildenafil on other medicinal products</u>

*In vitro studies*
Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 ($IC_{50}$ >150 µM). Given that sildenafil peak plasma concentrations, after the recommended doses, are approximately 1 µM, it is unlikely that sildenafil 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. Its co-administration with nitric oxide donors or nitrates is therefore contraindicated (see section 4.3).

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a small number of more susceptible patients. This is most likely to occur within 4 hours of taking sildenafil (see sections 4.2 and 4.4). In three specific drug-drug 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) who were already stabilised on doxazosin therapy. In these study populations, mean additional reductions in supine blood pressure of 7/7 mmHg, 9/5 mmHg and 8/4 mmHg, and mean additional reductions in standing blood pressure of 6/6 mmHg, 11/4 mmHg and 4/5 mmHg, 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 cases included dizziness or light-headedness, but not syncope.

No significant interactions were observed 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 acetylsalicylic 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.

The pooled analysis of all the data obtained on the following classes of antihypertensive medication: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (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, when sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, the mean additional reduction in supine systolic blood pressure was 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg.

These additional blood pressure reductions were of a similar magnitude to those observed when sildenafil was administered alone to healthy volunteers (see section 5.1).

Sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are cytochrome CYP3A4 substrates.

In healthy male volunteers, administration of 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 daily).

The addition of a single dose of sildenafil to sacubitril/valsartan at steady state in patients with hypertension was associated with a significantly greater reduction in blood pressure compared to the administration of sacubitril/valsartan alone. Therefore, caution should be exercised when initiating sildenafil treatment in patients taking sacubitril/valsartan.

**4.6 Fertility, pregnancy and lactation**

Sildenafil is not indicated for use by women.

There are no adequate and well-controlled studies in pregnant or breast-feeding 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 a single 100 mg oral dose of sildenafil in healthy volunteers (see section 5.1).

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

No studies have been conducted on 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 sildenafil, before driving or using machines.

**4.8 Undesirable effects**

Summary of the safety profile
The safety profile of sildenafil is based on 9,570 patients in 74 double-blind, placebo-controlled clinical trials. The most commonly reported adverse reactions in clinical trials among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, hot flush, visual disturbance, cyanopsia and blurred vision.

Adverse reactions reported during post-marketing surveillance of sildenafil have been gathered covering an estimated period of more than 10 years. Because not all adverse reactions have been reported to the marketing authorisation holder and included in the safety database, the frequencies of these adverse 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 (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), very rare (<1/10,000).

In addition, the frequency of clinically significant adverse reactions reported from post-marketing surveillance is included as frequency not known.

Within each frequency grouping, adverse reactions are listed in order of decreasing severity.

**Table 1: Clinically significant adverse reactions reported at an incidence greater than placebo in controlled clinical trials and clinically significant adverse reactions reported through post-marketing surveillance.**

| **System organ class** | **Very common** ***(≥1/10)*** | **Common** ***(≥1/100 and <1/10)*** | **Uncommon** ***(≥1/1,000 and <1/100)*** | **Rare** ***(≥1/10,000 and <1/1,000)*** |
|---|---|---|---|---|
| Infections and infestations | | | Rhinitis | |
| Immune system disorders | | | Hypersensitivity | |
| Nervous system disorders | Headache | Dizziness | Somnolence, hypoaesthesia | Cerebrovascular accident, transient |

| System organ class | Very common *(≥1/10)* | Common *(≥1/100 and <1/10)* | Uncommon *(≥1/1,000 and <1/100)* | Rare *(≥1/10,000 and <1/1,000)* |
|---|---|---|---|---|
| | | | | ischaemic attack, seizure*, seizure recurrence*, syncope |
| Eye disorders | | Visual colour distortions**, visual disturbance, blurred vision | Lacrimation disorders***, eye pain, photophobia, photopsia, ocular hyperaemia, visual brightness, conjunctivitis | Non-arteritic anterior ischaemic optic neuropathy (NAION)*, retinal vascular occlusion*, retinal haemorrhage, arteriosclerotic retinopathy, retinal disorder, glaucoma, visual field defect, diplopia, reduced visual acuity, 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 |
| Ear and labyrinth disorders | | | Vertigo, tinnitus | Deafness |
| Cardiac disorders | | | Tachycardia, palpitations | Sudden cardiac death*, myocardial infarction, ventricular arrhythmia*, atrial fibrillation, unstable angina |
| Vascular disorders | | Flushing, hot flush | Hypertension, hypotension | |
| Respiratory, thoracic and mediastinal disorders | | Nasal congestion | Epistaxis, sinus congestion | Throat tightness, nasal oedema, nasal dryness |
| Gastrointestinal disorders | | Nausea, dyspepsia | Gastroesophageal reflux disease, vomiting, abdominal pain upper, dry mouth | Oral hypoaesthesia |

| System organ class | Very common *(≥1/10)* | Common *(≥1/100 and <1/10)* | Uncommon *(≥1/1,000 and <1/100)* | Rare *(≥1/10,000 and <1/1,000)* |
|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | | | Rash | Stevens-Johnson syndrome (SJS)*, toxic epidermal necrolysis (TEN)* |
| Musculoskeletal and connective tissue disorders | | | Myalgia, limb pain | |
| Renal and urinary disorders | | | Haematuria | |
| Reproductive system and breast disorders | | | | Penile haemorrhage, priapism*, haematospermia, increased erection |
| General disorders and administration site conditions | | | Chest pain, fatigue, feeling hot | Irritability |
| Additional investigations | | | Increased heart rate | |

*Reported during post-marketing surveillance only
**Visual colour distortions: chloropsia, chromatopsia, cyanopsia, erythropsia and xanthopsia
***Lacrimation disorders: dry eye, lacrimal disorder and increased lacrimation

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 ratio of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form via the following link: https://sideeffects.health.gov.il/

**4.9 Overdose**

In studies in healthy volunteers with single 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 and altered vision) was increased.
In cases of overdose, standard supportive measures should be adopted. Renal dialysis is not expected to accelerate clearance of the drug as sildenafil 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.

Mechanism of action
Sildenafil is an oral therapy for the treatment of 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 corpora cavernosa during sexual stimulation. Nitric oxide activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpora cavernosa of the penis, allowing inflow of blood and subsequent filling.
Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpora cavernosa, 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 corpora cavernosa but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs during sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpora cavernosa levels of cGMP. Therefore, sexual stimulation is required in order for sildenafil to deliver its intended beneficial pharmacological effects.

Pharmacodynamic effects
Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. It has a 10-fold selectivity over PDE6, which is involved in the phototransduction mechanism in the retina. At maximum recommended doses, it has an 80-fold selectivity over PDE1 and 700-fold over PDE2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

Clinical efficacy and safety
Two clinical studies were specifically designed to assess the time window during which sildenafil could produce an erection in response to sexual stimulation. In a study using penile plethysmography (RigiScan) of fasted patients, the median time to onset for those who obtained erections of greater than 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-37 minutes) after sildenafil administration. In another RigiScan study, sildenafil was still able to produce an erection in response to stimulation 4-5 hours post-dose.

Sildenafil causes a mild and transient decrease in blood pressure which, in the majority of cases, does not translate into clinical effects. The mean maximum decrease in supine systolic blood pressure following a 100 mg oral dose of sildenafil was 8.4 mmHg and 5.5 mmHg in diastolic blood pressure. These decreases in blood pressure are consistent with the vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle. Single oral doses of sildenafil of up to 100 mg in healthy volunteers produced no clinically significant effects on the ECG.

In a study of the haemodynamic effects of a single oral 100 mg dose of sildenafil in 14 patients with severe coronary artery disease (>70% stenosis of at least one coronary artery), the mean resting systolic and diastolic blood pressures decreased by approximately 7% and 6% respectively compared to baseline. Mean pulmonary systolic blood pressure decreased by 9%. Sildenafil showed no effect on cardiac output, and did not impair blood flow through the stenosed coronary arteries.
A double-blind, placebo-controlled exercise stress trial evaluated 144 patients with erectile dysfunction and chronic stable angina who were regularly taking anti-anginal medicinal products (except nitrates). The results demonstrated no clinically significant differences between sildenafil and placebo in time to onset of angina.

Mild and transient differences in colour discrimination (blue/green) were detected in some patients using the Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident at 2 hours post-dose. The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. Sildenafil has no effect on visual acuity or contrast sensitivity. In a small size placebo-controlled study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100 mg) demonstrated no significant changes in the

visual tests conducted (visual acuity, Amsler grid, colour discrimination simulated traffic light, Humphrey perimeter and photostress).

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers (see section 4.6).

*Further information on clinical trials*
In clinical trials sildenafil was administered to more than 8,000 patients aged 19-87. The following patient groups were represented: elderly (19.9%), patients with hypertension (30.9%), diabetes mellitus (20.3%), ischaemic heart disease (5.8%), hyperlipidaemia (19.8%), spinal cord injury (0.6%), depression (5.2%), transurethral resection of the prostate (3.7%), radical prostatectomy (3.3%). The following groups were not well represented or were excluded from the clinical trials: patients with pelvic surgery, patients who had received radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions (see section 4.3).

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% (25 mg), 74% (50 mg) and 82% (100 mg) compared to 25% on placebo. In controlled clinical trials, the attrition rate due to sildenafil was low and similar to placebo. Across all clinical trials, the proportions of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischaemic heart disease (69%), hypertension (68%), transurethral resection of the prostate (TURP) (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long-term studies.

## 5.2 Pharmacodynamic 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 availability is 41% (range 25-63%). After oral dosing of sildenafil, AUC and $C_{max}$ increased in proportion with the 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 $t_{max}$ of 60 minutes and a mean reduction in $C_{max}$ of 29%.

Distribution
The mean steady state volume of distribution (Vd) for sildenafil is 105 L, indicating distribution of the medicinal product 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 a mean free plasma concentration for sildenafil of 18 ng/mL (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002% (average 188 ng) of the administered dose was detected in ejaculate 90 minutes after dosing.

Biotransformation
Sildenafil is metabolised predominantly by the CYP3A4 (principally) and CYP2C9 (to a lesser extent) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and the *in vitro* potency for PDE5 is approximately 50% that of the original active substance. 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 clearance of sildenafil is 41 L/hour, with a resultant terminal phase half-life of 3-5 hours. After oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

Pharmacokinetics in special patient groups

*Elderly*
Healthy elderly volunteers (65 years or older) had a reduced clearance of sildenafil, with approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite than those seen in healthy young volunteers (18-45 years). Due to the effect of ageing on plasma protein binding, the free sildenafil plasma concentration was approximately 40% higher.

*Renal insufficiency*
In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 mL/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. The mean AUC and $C_{max}$ of the N-desmethyl metabolite increased up to 126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance <30 mL/min), sildenafil clearance was reduced, with increases in AUC and $C_{max}$ of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and $C_{max}$ values were significantly increased by 200% and 79% respectively.

*Hepatic insufficiency*
In volunteers with mild to moderate 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. The pharmacokinetics of sildenafil in patients with severe hepatic impairment have not been studied.

### 5.3 Preclinical safety data

Data from non-clinical studies reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Masking flavour SC241160, peppermint flavour 501500 TP0504, hypromellose (15cp), anhydrous citric acid, xanthan gum, sucralose, acesulfame potassium (E-950), sodium benzoate, purified water.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The expiry date is indicated on the printing materials.
Shelf life after first opening: 12 months

### 6.4 Special precautions for storage

Store below $30^0$C.

### 6.5 Nature and contents of container

The primary packaging material of <Product name> consists of high density polyethylene (HDPE) bottles for 30 ml, provided with a child resistant closure composed of high density polyethylene (HDPE) cap and including a polypropylene metered pump of 0.5 ml per pump actuation.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Taro International LTD.
14 Hakitor St., Haifa Bay 2624761

## 8. MANUFACTURER

FARMALIDER S.A., C/ARAGONESES, 2 28108 ALCOBENDAS - MADRID, SPAIN

## 9. MARKETING AUTHORISATION NUMBER

Revised in June 2023 according to the MOH guidelines