1. NAME OF THE MEDICINAL PRODUCT

Viagra Connect Melts 50 mg orodispersible films

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible film contains sildenafil citrate equivalent to 50 mg of sildenafil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible film.

Thin pale red coloured orodispersible film (approximately 24 mm x 32 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Viagra Connect Melts is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Viagra Connect Melts to be effective, sexual stimulation is required.

4.2 Posology and method of administration

Posology

Use in adults
Viagra Connect Melts should be taken as needed approximately one hour before sexual activity. The recommended dose is 50 mg taken on an empty stomach as concomitant intake with food delays absorption and delays the effect of the orodispersible film (see section 5.2).
A significant delay in absorption is expected when orodispersible films are taken with a high fat meal compared to the fasted state (see section 5.2). It is recommended that orodispersible films be taken on an empty stomach. Orodispersible films can be taken with or without water.

Patients should be advised that they may need to take Viagra Connect Melts a number of times on different occasions (a maximum of one 50 mg film per day), before they can achieve a penile erection satisfactory for sexual activity. If after several attempts on different dosing occasions patients are still not able to achieve a penile erection sufficient for satisfactory sexual activity, they should be advised to consult a doctor.

Special populations

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

Renal impairment
No dosage adjustments are required for patients with mild to moderate renal impairment. However, since sildenafil clearance is reduced in individuals with severe renal impairment (creatinine clearance < 30 ml/min), individuals previously diagnosed with severe renal impairment must be advised to

consult their doctor before taking Viagra Connect Melts, since a 25 mg tablet may be more suitable for them (see section 4.4 for further information).

Hepatic impairment
Sildenafil clearance is reduced in individuals with hepatic impairment (e.g. cirrhosis). Individuals previously diagnosed with mild to moderate hepatic impairment must be advised to consult their doctor before taking Viagra Connect Melts, since a 25 mg tablet may be more suitable for them (see section 4.4 for further information). The safety of sildenafil has not been studied in patients with severe hepatic impairment, and its use is therefore contraindicated (see section 4.3).

Paediatric population
Viagra Connect Melts is not indicated for individuals below 18 years of age.

Use in patients taking other medicinal products
Pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, erythromycin, cimetidine).

With the exception of ritonavir, for which co-administration with sildenafil is contraindicated (see section 4.3), individuals receiving concomitant treatment with CYP3A4 inhibitors must be advised to consult their doctor before taking Viagra Connect Melts, since a 25 mg tablet may be more suitable for them (see section 4.4 for further information).

In order to minimise the potential of developing postural hypotension in patients receiving alpha blocker treatment (e.g. alfuzosin, doxazosin or tamsulosin), patients should be stabilised on alpha blocker therapy prior to initiating sildenafil treatment. Thus, patients taking alpha blockers must be advised to consult their doctor before taking Viagra Connect Melts since a 25 mg tablet may be more suitable for them (see sections 4.4 and 4.5).

Method of administration

For oral use.

The aluminium pouch should be carefully peeled open (and not cut open). The orodispersible film should be taken out with a dry finger, placed on the tongue and allowed to disintegrate with or without water. During disintegration saliva may be swallowed, but without swallowing the film. It should be taken immediately upon removal from the pouch.

A significant delay in absorption is expected when orodispersible films are taken with a high fat meal compared to the fasted state (see section 5.2). It is recommended that orodispersible films be taken on an empty stomach. Orodispersible films can be taken with or without water.

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.

Co-administration of Viagra Connect Melts with ritonavir (a highly potent P450 enzyme inhibitor) is contraindicated (see section 4.5).

The co-administration of phosphodiesterase type 5 (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).

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used by those men for whom sexual activity may be inadvisable, and these patients should be referred to their doctor. This includes patients with severe cardiovascular disorders such as a recent (6 months) acute myocardial infarction (AMI) or stroke, unstable angina or severe cardiac failure.

Sildenafil should not be used in patients with severe hepatic impairment, hypotension (blood pressure < 90/50 mmHg) and known hereditary degenerative retinal disorders such as *retinitis pigmentosa* (a minority of these patients have genetic disorders of retinal phosphodiesterases). This is because the safety of sildenafil has not been studied in these sub-groups of patients, and its use is therefore contraindicated.

Sildenafil 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).

Viagra Connect Melts should not be used in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

Viagra Connect Melts is not indicated for use by women.

The medicinal product is not intended for men without erectile dysfunction.

This medicinal product is not intended for men under 18 years of age.

4.4 Special warnings and precautions for use

Erectile dysfunction can be associated with a number of contributing conditions, e.g. hypertension, *diabetes mellitus*, hypercholesterolaemia or cardiovascular disease. As a result, all men with erectile dysfunction should be advised to consult their doctor within 6 months for a clinical review of potential underlying conditions and risk factors associated with erectile dysfunction (ED). If symptoms of ED have not improved after taking Viagra Connect Melts on several consecutive occasions, or if their erectile dysfunction worsens, the patient should be advised to consult their doctor.

Cardiovascular risk factors
Since there is a degree of cardiac risk associated with sexual activity, the cardiovascular status of men should be considered prior to initiation of therapy.

Agents for the treatment of erectile dysfunction, including sildenafil, are not recommended to be used by those men who with light or moderate physical activity, such as walking briskly for 20 minutes or climbing 2 flights of stairs, feel very breathless or experience chest pain.

The following patients are considered at low cardiovascular risk from sexual activity: patients who have been successfully revascularised (e.g. via coronary artery bypass grafting, stenting, or angioplasty), patients with asymptomatic controlled hypertension, and those with mild valvular disease. These patients may be suitable for treatment but should consult a doctor before resuming sexual activity.

Patients previously diagnosed with the following must be advised to consult with their doctor before resuming sexual activity: uncontrolled hypertension, moderate to severe valvular disease, left ventricular dysfunction, hypertrophic obstructive and other cardiomyopathies, or significant arrhythmias.

Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis), or those with the rare syndrome of multiple system atrophy

manifesting as severely impaired autonomic control of blood pressure. Men with these conditions must not use the medicinal product without consulting a doctor.

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
Patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia), should consult a doctor before using agents for the treatment of erectile dysfunction, including sildenafil.

Prolonged erections and priapism have been occasionally 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 (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 Viagra Connect Melts and consult a physician immediately (see section 4.3).

Concomitant use with CYP3A4 inhibitors
Pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, itraconazole, erythromycin, cimetidine). Although, no increased incidence of adverse events was observed in these patients, they should be advised to consult a doctor before taking Viagra Connect Melts as a 25 mg tablet may be more suitable for them (see section 4.5 for further information).

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. Thus, patients taking alpha blockers should be advised to consult their doctor before taking Viagra Connect Melts as a 25 mg tablet may be more suitable for them. Treatment should be stopped if symptoms of postural hypotension occur, and patients should seek advice from their doctor on what to do.

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 the use of sildenafil is not recommended in those patients with history of bleeding disorders or active peptic ulceration, and should only be administered after consultation with a doctor.

Hepatic impairment
Patients with hepatic impairment must be advised to consult their doctor before taking Viagra Connect Melts, since a 25 mg tablet may be more suitable for them (see section 4.2 and 5.2 for further information).

Renal impairment
Patients with severe renal impairment (creatinine clearance < 30 mL/min), must be advised to consult their doctor before taking Viagra Connect Melts, since a 25 mg tablet may be more suitable for them (see section 4.2 and 5.2 for further information).

Use with alcohol
Drinking excessive alcohol can temporarily reduce a man's ability to get an erection. Men should be advised not to drink large amounts of alcohol before sexual activity.

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 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
Pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, with the exception of individuals taking ritonavir for which co-administration with sildenafil is contraindicated, individuals must be advised to consult their doctor before taking Viagra Connect Melts, since a 25 mg tablet may be more suitable for them.

Co-administration of the 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 had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results sildenafil should not be co-administered with ritonavir (see section 4.3).

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 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 specific 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 medicinal products, 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 medicinal products

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 sildenafil peak plasma concentrations of approximately 1 μM after 100 mg of sildenafil, it is unlikely that Viagra Connect Melts 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).

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 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) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of 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 stabilized 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 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, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 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 seen 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 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 two times a day).

Addition of a single dose of sildenafil to sacubitril/valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of sacubitril/valsartan alone. Therefore, caution should be exercised when sildenafil is initiated in patients treated with sacubitril/valsartan.

4.6 Fertility, pregnancy and lactation

Viagra Connect Melts 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 single 100 mg oral doses of sildenafil in healthy volunteers (see section 5.1).

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 this medicine, before driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

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

Adverse reactions from post-marketing surveillance has been gathered covering an estimated period

> 10 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). 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	**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)***
Infections and infestations			Rhinitis	
Immune system disorders			Hypersensitivity	
Nervous system disorders	Headache	Dizziness	Somnolence, Hypoaesthesia	Cerebrovascular accident, Transient ischaemic attack, Seizure,* Seizure recurrence,* Syncope
Eye disorders		Visual colour distortions**, Visual disturbance, Vision blurred	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, 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 discoloration
Ear and labyrinth disorders			Vertigo, Tinnitus	Deafness

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)***
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	Gastro oesophagael reflux disease, Vomiting, Abdominal pain upper, Dry mouth	Hypoaesthesia oral
Skin and subcutaneous tissue disorders			Rash	Stevens-Johnson Syndrome (SJS)*, Toxic Epidermal Necrolysis (TEN)*
Musculoskeletal and connective tissue disorders			Myalgia, Pain in extremity	
Renal and urinary disorders			Haematuria	
Reproductive system and breast disorders				Penile haemorrhage, Priapism*, Haematospermia, Erection increased
General disorders and administration site conditions			Chest pain, Fatigue, Feeling hot	Irritability
Investigations			Heart rate increased	

*Reported during post-marketing surveillance only
**Visual colour distortions: Chloropsia, Chromatopsia, Cyanopsia, Erythropsia and Xanthopsia
***Lacrimation disorders: Dry eye, Lacrimal disorder and Lacrimation 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. Healthcare professionals are asked to report any suspected adverse reactions via directly via
ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

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 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 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.

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. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At 100 mg doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE 2, 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
A clinical study was specifically designed to assess the time window after dosing during which sildenafil could produce an erection in response to sexual stimulation. In a penile plethysmography (RigiScan) study of sildenafil 50 mg in fasted patients, the median time to onset for those who obtained erections of 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-37 minutes) on sildenafil.

Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing of sildenafil was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. 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 up to 100 mg in healthy volunteers produced no clinically relevant effects on 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 (CAD) (>70% stenosis of at least one coronary artery), the mean resting systolic and diastolic blood pressures decreased by 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 regularly received anti-anginal medicinal products (except nitrates). The results, following a 100 mg dose, demonstrated no clinically relevant differences between sildenafil and placebo in time to limiting angina.

Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident after 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 (doses 25 to 100 mg) was administered to more than 8000 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 excluded from clinical trials: patients with pelvic surgery, patients post-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 discontinuation rate due to sildenafil was low and similar to placebo.

Across all trials, the proportion 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%), TURP (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long term studies.

Four clinical trials (148-102, 148-364 and 101/101B and A1481239) each directly compared the efficacy of fixed 50 mg doses of sildenafil and double-blind placebo, each taken approximately 1 hour prior to sexual activity by men with ED for treatment periods lasting 8-24 weeks. Efficacy was assessed by means of diaries used to capture details of each sexual event, and a sexual function questionnaire (now known as the International Index of Erectile Function) IIEF. Men were told that sexual stimulation was necessary for efficacy to occur, and that erections would not occur in absence of sexual stimulation. Compared to placebo, sildenafil 50 mg caused clinically and statistically

significant improvements in proportions of erections hard enough for sexual intercourse and erections lasting long enough to complete sexual intercourse. All the following results with sildenafil 50 mg were also clinically and statistically significantly different from placebo unless otherwise stated. Sildenafil 50 mg improved the men's confidence to get and keep an erection. Sildenafil 50 mg also improved men's satisfaction with sexual intercourse, orgasm, sexual relationship with partner and overall sex life. Sildenafil 50 mg had no clinically significant effect on sexual desire. Men (in whom sildenafil 50 mg was effective) reported improved function (increased hardness of erection with duration long enough to complete intercourse) after the first dose (40.8% for 50 mg and 14.6% for placebo). However some men only reported improvements after several (up to 8) doses (78.4% for 50 mg and 46.7% for placebo). Sildenafil 50 mg was effective at various times post-dose from less than 1 hour to up to 4 hours after administration. In the two studies that included assessment of quality of life (148-102, 148-364), men treated with sildenafil reported less distress associated with erection problems than men receiving placebo. One study (A1481239) used additional questionnaires to evaluate the effect of sildenafil on sexual performance and relationship with partner. In this study men taking sildenafil 50 mg 30 minutes to one hour prior to sexual activity reported improved quality of erections and satisfaction with sexual experience, improved relationship with partner, improved confidence and self–esteem and less anxiety about attempting sexual intercourse than men taking placebo. Effectiveness and satisfaction with treatment is maintained during follow on long-term treatment (one year and longer) (study 148-101C). In the study (148-101B) assessing partner satisfaction with intercourse, female partners of men treated with sildenafil 50 mg reported improved satisfaction with sexual intercourse compared to partners of men treated with placebo.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing sildenafil in all subsets of the paediatric population for the treatment of erectile dysfunction (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Film-coated tablets
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 C_{max} 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 t_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

Orodispersible films
In a clinical study in 80 healthy males 20-43 years of age, sildenafil 50 mg orodispersible films administered without water were observed to be bioequivalent to the sildenafil 50 mg film-coated tablets.

In another study in 40 healthy males 23-54 years of age, sildenafil 50 mg orodispersible films administered with water were observed to be bioequivalent to the sildenafil 50 mg film-coated tablets.

The effect of food on sildenafil 50 mg orodispersible films has not been studied, however an effect of food is expected (see section 4.2).

When orodispersible tablets are taken with a high fat meal, the rate of absorption of sildenafil is reduced, median t_{max} is delayed by about 3.4 hours and mean C_{max} and AUC are reduced respectively by about 59% and 12%, compared to administration of orodispersible tablets under fasting conditions.

Distribution

The mean steady state volume of distribution (V_d) 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.

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 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).

Pharmacokinetics in special patient groups

Elderly
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal impairment
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 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, resulting in mean 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 200% and 79% respectively.

Hepatic impairment
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (85%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose (E 463)
Macrogol
Crospovidone (E 1202)
Povidone (E 1201)
Sucralose (E 955)
Macrogol poly(vinyl alcohol) grafted copolymer
Levomenthol
Hypromellose (E 464)
Titanium dioxide (E 171)
Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each orodispersible film is individually packed in a heat-sealed polyethylene-lined aluminium pouch.
Supplied in cartons containing 2, 4, or 8 pouches.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Viatris Hellas Ltd
253-255, Mesogion Avenue,
154 51 Neo Psychiko,
Athens, Greece

8. MARKETING AUTHORISATION NUMBER(S)

MA1396/01402

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17th July 2025

10. DATE OF REVISION OF THE TEXT

26th June 2025