SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

(Sildenafil citrate tablets 100 mg)

1.1 Strength

100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative declaration

Sildenafil Citrate* USP 142.00 - Active

3. PHARMACEUTICAL FORM

Oral Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

4.1 Sildenafil citrate 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 sildenafil citrate to be effective, sexual stimulation is required.

4.2 Posology and method of administration

Posology Use in adults The recommended dose is 100 mg taken as needed approximately one hour before sexual activity. Based on efficacy and tolerability, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If Sildenafil citrate is taken with food, the onset of activity may be delayed compared to the fasted state. Special populations Elderly Dosage adjustments are not required in elderly patients (≥ 65 years old). Renal impairment The dosing recommendations described in “Use in adults” apply 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 should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 100 mg up to 100 mg as

necessary. Hepatic impairment Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 100 mg up to 100 mg as necessary. Paediatric population Sildenafil citrate is not indicated for individuals 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 a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors. In order to minimise the potential of developing postural hypotension in patients receiving alpha-blocker treatment patients should be stabilised on alpha-blocker therapy

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Product Name Sildenafil citrate tablets 100 mg prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered. Method of administration For oral use

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate

(cGMP) pathway, sildenafil was shown to potentiate the hypotensive effects of

nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated. 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. Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure). Sildenafil citrate 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. The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: 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 should be undertaken to diagnose erectile dysfunction and PHARMACOKINETIC PROPERTIES determine potential underlying causes, before pharmacological treatment is considered. Absorption Cardiovascular risk factors Sildenafil Is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has 41% (range 25-63%). after oral dosing of sildenafil AUC and Cmax increase in proportion with dose over vasodilator properties, resulting in mild and transient decreases the recommended dose range (25-100 mg). in blood pressure. Prior to prescribing sildenafil, physicians should carefully consider whether their When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in tmax of 60 patients with certain underlying conditions could be adversely affected by such vasodilator effects, minutes and a mean reduction in Cmax of 29%. especially in combination with sexual activity. Patients with increased susceptibility to vasodilators Distribution include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive The mean steady state volume of distribution (Vd) for sildenafil is 105 I, indicating distribution into the cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is impaired autonomic control of blood pressure. approximately 440 ng/mL (CV 40%). Since sildenafil (and its major circulating N-dimethyl metabolite) is Priapism 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil Agents for the treatment of erectile dysfunction, including sildenafil, should be used with caution in of 18 ng/mL (38 nM). Protein binding is independent of total drug concentrations. patients with anatomical

deformation of the penis (such as angulation cavernosal fibrosis or Peyronie's In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002% (average 188 mg) of disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell the administered dose was present in ejaculate 90 minutes after dosing. anaemia, multiple myeloma or leukaemia). Biotransformation Effects on vision Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. other PDE5 inhibitors. Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for been reported spontaneously and in an observational study in connection with the intake of sildenafil and PDE5 approximately 50% tat of the parent drug. Plasma concentrations of this metabolite are other POE5 inhibitors. Patients should be advised that in the event of any sudden visual defect, they approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolized, with should stop taking Sildenafil and consult a physician immediately. a terminal halt-life of approximately 4 h. Concomitant use with ritonavir Elimination Co-administration of sildenafil with ritonavir is not advised. The total body clearance of sildenafil A 41 L/h with a resultant terminal phase hail-life of 3-5 h. After Concomitant use with alpha-blockers either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faces Caution is advised when sildenafil is administered to patients taking an alpha- blocker as the co- (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administration may lead to symptomatic hypotension in a few susceptible individuals. This is most likely administered oral dose). to occur within 4 hours post sildenafil dosing. In order to minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating PRESENTATION sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered. In addition, DENEGRA 50: Carton containing 1 blister of 4 tablets along with pack insert. physicians should advise patients what to do in the event of postural hypotensive

symptoms. DENEGRA 100: Carton containing 1 blister of 1 tablet along with pack inserts. Effect on bleeding OR Carton containing 4 blisters of 1 tablet along with pack inserts. 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, sildenafil should be administered to these STORAGE CONDITION: patients only after careful benefit-risk assessment. Store below 30°C. Protect from light & moisture. Women Sildenafil is not indicated for use by women. Keep medicine out of the reach and sight of children. 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 Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, and 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. 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. Manufactured for

DEN MARK Manufactured By PHARMACEUTICALS PVT. LTD. RATNATRIS PHARMACEUTICALS PVT. LTD. First Floor Harish Textiles, Parsi Panchayat Road, Survey No. 416, At. - Indrad, Ta. - Kadi, Andheri East, Mumbai-400069, INDIA. Dist. - Mehsana, Pin.- 382715 Gujarat, India. Product Name Sildenafil citrate tablets 100 mg

1.4 Product Information

1.4.1 Prescribing information ( )

4.5 Interaction with other medicinal products and other forms of interaction

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 and 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 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 Cmax 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 co-administration of sildenafil with ritonavir is not advised and, in any event, the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours. 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 Cmax and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. 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

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 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, Cmax, tmax, 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 (100 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, 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 Cmax, 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 (IC50 >150 µM). Given sildenafil peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely that SILDENAFIL CITRATE 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, 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. 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.

Product Name Sildenafil citrate tablets 100 mg Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated. 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. In three specific drug-drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 100 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 (100 mg) was co-administered with tolbutamide (2100 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9. Sildenafil (100 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (1100 mg). Sildenafil (100 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, betablockers, 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. 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 t.i.d.) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan Cmax (125 mg b.i.d.). Additional information on special populations Not Applicable Paediatric population Not Applicable

4.6 Fertility, pregnancy and lactation

Product Name Sildenafil citrate tablets 100 mg Sildenafil citrate 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..

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 repo Sildenafil citrate, before driving or operating machinery.

4.8 Undesirable effects

THERAPEUTIC INDICATIONS: Infections and infestations:Rhinitis Sildenafil is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain Immune system disorders:Hypersensitivity a penile erection sufficient for satisfactory sexual performance. In order for Sildenafil to be effective, Nervous system disorders:Headache, Dizziness, Somnolence, Hypoesthesia, Cerebrovascular accident, sexual stimulation is required. Transient ischemic attack Seizure, Seizure recurrence, Syncope. Eye disorders:Visual colour distortions, Visual disturbance, Vision blurred, Lacrimation disorders, Eye POSOLOGY AND METHOD OF ADMINISTRATION: pain, Photophobia, Photopia, Ocular hyperemia, Visual

brightness, Conjunctivitis, Non-arteritic anterior Use in adults Ischaemic optic neuropathy (NAION)", Retinal vascular occlusion*, Retinal hemorrhage, Arteriosclerotic The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based retinopathy, Retinal disorder, Glaucoma, Visual field defect, Diplopia, Visual acuity reduced, Myopia, on efficacy and tolerability, the dose may be increased to 100 mg or decreased to 25 mg. The maximum Asthenopia, Vitreous floaters, Iris disorder, Mydriasis, Halo vision, Eye oedema, Eye swelling, Eye recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If disorder, Conjunctival hyperemia, Eye irritation, Abnormal sensation in eye, Eyelid oedema, Scleral Sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state. discoloration Special populations Ear and labyrinth disorders:Vertigo, Tinnitus, Deafness Elderly Cardiac disorders:Tachycardia, Palpitations, Sudden cardiac death, Myocardial Infarction, Ventricular Dosage adjustments are not required in elderly patients (≥ 65 years old). arrhythmia, atrial fibrillation, unstable angina Renal impairment Vascular disorders:Flushing, Hot flush, Hypertension, Hypotension, The dosing recommendations described in 'Use in adult' apply to patients with mild to moderate renal Respiratory, thoracic and mediastinal disorders:Nasal congestion, Epistaxis, Sinus congestion, Throat impairment (creatinine clearance = 30-80 mL/min). Since sildenafil clearance is reduced in patients with tightness, Nasal oedema, Nasal dryness severe renal impairment (creatinine clearance <30 mL/min) a 25 mg dose should be considered. Based on Gastrointestinal disorders:Nausea, Dyspepsia, Gastro esophageal reflex disease, Vomiting, Abdominal efficacy and tolerability, the dose may be increased step-wise to 50 mg up to 100 mg as necessary. pain upper, Dry mouth, Hypoesthesia oral Hepatic Impairment Skin and subcutaneous tissue disorders:Rash, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose (TEN) should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg up Musculoskeletal and connective tissue disorders:Myalgia, Pain in extremity to 100 mg as necessary. Renal and urinary disorders:Haematuria Reproductive system and breast disorders:Penile haemorrhage, Priapism, Haematospermia, Erection Paediatric population increased Sildenafil is not indicated for individuals below 18 years of age. General disorders

and administration site conditions:Chest pain, Fatigue, Feeling hot: Use In patients taking other medicinal products With the exception of ritonavir for which co-administration with sildenafil is not advised a starting dose OVERDOSE of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors. In In single dose volunteer studies of doses up to 800 mg, adverse reactions were similar to those seen at order to minimize the potential of developing postural hypotension in lower doses, but the incidence was and severities were increased. Doses of 200 mg did not result in Patient receiving alpha-blocker treatment, patients should be stabilized on alpha-blacker therapy prior to increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered. congestion, altered vision) was increased. In cases of overdose, Standard supportive measures should be Method at administration: adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to For oral use. plasma proteins and not eliminated in the urine. CONTRAINDICATIONS PHARMACOLOGICAL PROPERTIES Hypersensitivity to the active substance or to any of the excipients. Pharmacodynamics properties Consistent with its known effects on the nitric oxide /cyclic guanosine monophosphate (cGMP) pathway, Pharmacotherapeutic group: Urological; Drugs used in erectile dysfunction Sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric Mechanism of action oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated. · Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, The co-administration of POE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such it restores impaired erectile function by increasing blood flow to the penis. as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension. · The physiological mechanism responsible for erection of the penis involves the release of nitric oxide Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or guanylate cyclase, which results in increased levels of cyclic guanosine

monophosphate (cGMP), severe cardiac failure). producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil is contraindicated in patients who have loss of vision in one eye because of non-arteritic · Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of not wit previous PDE5 inhibitor exposure. cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on The safety of sildenafil has not been studied in the following sub-groups of patients and its use is isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. Therefore contraindicated: severe hepatic impairment, hypotension (blood pressure <90/50 mmHg), · When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required as retinas pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases). in order for sildenafil to produce its intended beneficial pharmacological effects.

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: G04BE03

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.

Product Name Sildenafil citrate tablets 100 mg 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 maximum recommended 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.

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 41% (range 25-63%). After oral dosing of sildenafil AUC and Cmax increase in proportion with dose over the recommended dose range (25-100 mg). When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in tmax of 60 minutes and a mean reduction in Cmax of 29%. Distribution The mean steady state volume of distribution (Vd) for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/mL (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/mL (38 nM). Protein binding is independent of total drug concentrations. 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 halflife 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).

5.3 Pre-clinical 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.

5.3 Preclinical safety data

Not provided in the source SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not provided in the source SmPC.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

4 tablets packed in an Alu-PVC blister, pack such 1 blister in carton with an insert

. 1tablets packed in an Alu-PVC blister, pack such 1 blister in carton with an insert

6.6 Special precautions for disposal and other handling

Not applicable.

Product Name Sildenafil citrate tablets 100 mg

Kadi, Dist. - Mehsana, Pin-382715 Gujarat, India.

7. MARKETING AUTHORISATION HOLDER

DEN MARK PHARMACEUTICALS PVT.LTD. First Floor Harish Textiles Parsi Panchayat Road, Andheri East, Mumbai-400069, India

Manufacturing Site Addresses:

RATNATRIS PHARMACEUTICALS PVT. LTD. Survey No. 416, At. - Indrad, Ta. -

Not provided in the source SmPC.

8. MARKETING AUTHORISATION NUMBER(S)

H2022/CTD10582/22929

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2023 November 01

10. DATE OF REVISION OF THE TEXT

2023 November 01