

### 1.3.1 Summary of product characteristics (SmPC)

## 1. NAME OF THE MEDICINAL PRODUCT

**1.1 Product Name : VENEGRAY 50 TABLETS**

**1.2 Generic Name : Sildenafil Citrate Tablets 50 mg**

**1.3 Strength : 50 mg**

**1.4 Pharmaceutical Form : Film Coated Tablet**

**1.5 Packaging : 1 X 4 Alu-PVC Blister pack and 2 X 4 Alu-PVC Blister pack.**

## 2. QUALITY AND QUANTITATIVE COMPOSITION

**Batch size: 7.55 Lac.**

Sr. No.	Ingredients	Reference	Qty./tab (mg)	Function
<b>DRY MIXING</b>				
1.	Sildenafil citrate	BP	70.00	Active
2.	Maize Starch	BP	240.00	Binder
3.	Microcrystalline Cellulose powder	BP	20.00	Anticaking agent
4.	Dicalcium Phosphate	BP	138.25	Diluent
<b>BINDING</b>				
6.	PVPK 30	BP	3.25	Binder
7.	Isopropyl alcohol	BP	*32.50	Solvent
8.	Maize Starch	BP	25.00	Binder
9.	Sodium Methyl Paraben	BP	0.83	Preservative
10.	Sodium Propyl Paraben	BP	0.42	Preservative
11.	Purified Water	BP	*225.00	Vehicle

LUBRICATION				
12.	Talcum	BP	18.20	Anticaking agent
13.	Colloidal silicon dioxide (AEROSIL 200)	BP	2.00	Disintegrant
14.	Magnesium Stearate	BP	21.25	Lubricant
15.	Cros Carmellose Sodium	BP	18.00	Disintegrant
16.	Sodium Starch Glycolate	BP	17.80	Suspending agent
COATING				
17.	Methylene Dichloride	BP	**197.92	Solvent
18.	Novomix White Glow	IH	0.25	Coating agent
19.	Isopropyl alcohol	BP	*197.92	Solvent
20.	PVPK 30	BP	1.27	Binder
21.	Ultracoat U WTIC 30 Blue	IH	17.11	Colouring agent

**Legend:**

BP = British Pharmacopoeia

IP = Indian Pharmacopoeia

IH = In-House Specification

USP = United States Pharmacopoeia

\*Isopropyl alcohol and Purified water are evaporated during drying process, so it has negligible impact on average weight of tablet.

\*\*Methylene Dichloride is also evaporated during drying process, so it has negligible impact on average weight of tablet.

Average weight of the tablet is 593.63 mg.

### 3. PHARMACEUTICAL FORM

#### VISUAL DESCRIPTION:

Blue coloured, Diamond shape, Film coated tablet plain on one side and Digit “50” embossed on the other side of each tablet.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications:

Treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile

erection sufficient for satisfactory sexual performance.

#### **4.2 Posology and method of administration**

The usual starting dose of Sildenafil is 50 mg once daily. It should be taken before 30-40 minutes of intercourse. Depending on effectiveness and tolerance; the dose may be increased to a minimum recommended dose of 100 mg or decreased to 25 mg. The maximum dosing frequency is once per day. Some factors are associated with increased plasma levels of Sildenafil: age > 65, hepatic impairment, severe renal impairment and concomitant use of ketoconazole, itraconazole and erythromycin. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients. **VENEGRAY 50 TABLETS (Sildenafil Citrate Tablets 50 mg)** may take longer time to work if you take it with a heavy meal.

#### **Method of administration**

Oral administration

#### **4.3 Contraindications**

**VENEGRAY 50 TABLETS (Sildenafil Citrate Tablets 50 mg)** was shown to potentiate the hypotensive effects of nitrate and its administration to patients who are using organic nitrates, either regularly and or intermittently in any form is therefore contraindicated.

#### **4.4 Special warnings and precautions for use:**

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

#### **Cardiovascular risk factors**

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure. Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

**VENEGRAY 50 TABLETS (Sildenafil Citrate Tablets 50 mg)** potentiates the hypotensive effect of nitrates. 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 **VENEGRAY 50 TABLETS (Sildenafil Citrate Tablets 50 mg)**. 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 **VENEGRAY 50 TABLETS (Sildenafil Citrate Tablets 50 mg)** without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

### **Priapism**

Agents for the treatment of erectile dysfunction, including sildenafil, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

### **Concomitant use with other treatments for erectile dysfunction**

The safety and efficacy of combinations of sildenafil with 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. 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. Patients should be advised that in case of sudden visual defect, they should stop taking **VENEGRAY 50 TABLETS (Sildenafil Citrate Tablets 50 mg)** and consult a physician immediately.

### **Concomitant use with ritonavir**

Co-administration of sildenafil with ritonavir is not advised.

### **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. This is most likely 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 sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered. In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

## **45 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.

### **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.

Sildenafil had no effect on ritonavir pharmacokinetics. Based on 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.

Sildenafil had no effect on HIV protease inhibitor saquinavir pharmacokinetics.

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<sub>max</sub>, t<sub>max</sub>, 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, population pharmacokinetic analysis showed no effect of concomitant medication 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).

### **4.6 Pregnancy and lactation**

Sildenafil is not indicated for use by women.

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

No studies on the effects on the ability to drive and use machines have been performed. As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to Sildenafil, before driving or operating machinery.

### **4.8 Undesirable/side effects**

Like all medicines, Sildenafil can cause side effects although not everybody gets them. The side effects of Sildenafil are usually mild to moderate and of a short duration. All medicines including

Sildenafil can cause allergic reactions. Contact with doctors immediately if experiences any of the following symptoms after taking Sildenafil: sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat. Common side effect includes headache, facial flushing, indigestion, effects on vision, light sensitivity, blurred vision or reduced stuffy nose and dizziness.

#### **4.9 Overdose**

In single dose volunteer studies of doses up to 800 mg with sildenafil tablets, adversereactions 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.

### **Pharmacological properties**

#### **4.10 Pharmacodynamic properties**

**Pharmacotherapeutic group:** 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.

#### **4.11 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%).

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 tablets (100 mg single dose), less than 0.0002% (average 188 mg) 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 metabolized, 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 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 Cmax 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 Cmax of 100% and 88% respectively compared to age-matched volunteers with no renal

impairment. In addition, N-desmethyl metabolite AUC and C<sub>max</sub> values were significantly increased 79% and 200% 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<sub>max</sub> (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function has not been studied.

#### **4.12 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.

### **5. PHARMACEUTICAL PARTICULARS:**

#### **5.1 List of Excipients**

<b>Sr. No.</b>	<b>Name of the Excipient</b>	<b>Function</b>
1.	Microcrystalline Cellulose	Diluent
2.	Dicalcium Phosphate	Diluent
3.	Maize Starch	Binder
4.	PVP K30	Binder
5.	Iso Propyl Alcohol	Solvent
6.	Sodium Methyl Paraben	Preservative
7.	Sodium Propyl Paraben	Preservative
8.	Talcum	Anticaking agent
9.	Colloidal Silicon Dioxide (Aerosil-200)	Disintegrant
10.	Magnesium Stearate	Lubricant
11.	Cros Carmellose Sodium	Lubricant
12.	Sodium Starch Glycolate	Disintegrant



**Brand Name: VENEGRAY 50 TABLETS**  
**Generic Name: Sildenafil Citrate Tablets 50 mg**

13.	Methylene Dichloride	Coating Solvent
14.	Novomix White Glow	Coating Agent
15.	Ultracoat UWTIC 30 Blue	Colour

**52 Shelf life**

36 Months

**53 Special precautions for storage**

Store at a temperature not exceeding 30°C in a dry place. Keep the medicines out of reach of children.

**54 Nature and contents of container**

1 x 4 and 2 x 4 Diamond shape tablets in Alu-PVC Blister pack mono carton with pack insert, such 25 mono-cartons are packed in Shrink Sleeves and further packed in corrugated box.

**55 Special precautions for disposal and other handling**

No special requirements.

**6. MANUFACTURER:**

**WINTECH PHARMACEUTICALS LTD.**

Plot No 45-46, STICE, Musalgaon,

Tal. Sinnar, Nashik-422112,

MAHARASHTRA STATE, INDIA.

**7. DISTRIBUTED BY:**

**YELLOW PHARMACEUTICAL CO. LTD.**

**Address:** 10, Ewulobia Street,

Owaliwo Layout, Onitsha

Anambra State, Nigeria.