SUMMARY OF PRODUCT CHARACTERISTICS

COMIT 100

1. NAME OF THE MEDICINAL PRODUCT

Comit 100 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains

Sildenafil Citrate equivalent to sildenafil 100 mg

3. PHARMACEUTICAL FORM

Film-coated tablet

White tetragonal biconvex tablets having one side '100' embossed & other side in plain.

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.

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

4.2 Posology and method of administration

For oral use.

Use in adults and elderly

The recommended dose is 50mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100mg or decreased to 25mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If Sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state.

Use in patients with impaired renal function

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 25mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50mg and 100mg.

Use in patients with impaired hepatic function

Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50mg and 100mg.

Use in children and adolescents

Sildenafil is not indicated for individuals below 18 years of age.

4.3 Contraindications

Comit-100 is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

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 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.

4.4 Special warnings and precautions for use

A medical history and physical examination should be undertaken to diagnose cases such as erectile Dysfunction, cardiovascular status, left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), multiple system atrophy manifesting as severely impaired autonomic control of blood pressure, anatomical deformation of the penis

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be taken while administering Sildenafil Citrate concomitantly with drugs such as cytochrome P450 (CYP) inhibitors, CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine), HIV protease inhibitor (ritonavir, saquinavir), CYP3A4 inhibitor (erythromycin), grape juice, nicorandil and nitrates.

4.6 Fertility, pregnancy and lactation

Sildenafil is not indicated for use by women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

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 effects

The safety profile of Sildenafil is based on 8691 patients who received the recommended dosing regimen in 67 placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, visual disorders, nasal congestion, dizziness and visual colour distortion.

Rarely side effects such as hypersensitivity reactions, somnolence, hypoaesthesia, cerebrovascular accident, syncope, transient ischaemic attack, seizure, seizure recurrence, conjunctival disorders, eye disorders, non-arteritic anterior ischaemic optic neuropathy (NAION), retinal vascular occlusion, visual field defect, vertigo, tinnitus, deafness, flushing, hypertension, hypotension, palpitations, tachycardia, myocardial infarction, atrial fibrillation, ventricular arrhythmia, unstable angina, nasal congestion, epistaxis, dyspepsia, vomiting, nausea, dry mouth, skin rash, epidermal necrolysis (TEN), myalgia, haematuria, haematospermia, penile haemorrhage, priapism, prolonged erection, chest pain, fatigue and increased heart rate.

4.9 Overdose

In single dose volunteer studies of doses up to 800mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased.

Doses of 200mg 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

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.

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. Two clinical studies were 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 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. In a separate RigiScan study, sildenafil was still able to produce an erection in response to sexual stimulation 4-5 hours post-dose. 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 100mg 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 100mg in healthy volunteers produced no clinically relevant effects on ECG.

In a study of the hemodynamic effects of a single oral 100mg 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.

No clinical relevant differences were demonstrated in time to limiting angina for sildenafil when compared with placebo in a double blind, placebo controlled exercise stress trial in 144 patients with erectile dysfunction and chronic stable angina, who were taking on a regular basis anti-anginal medications (except nitrates).

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 100mg 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, 100mg) demonstrated no significant changes in 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 100mg oral doses of sildenafil in healthy volunteers.

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 (25-100mg). 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 (100mg single dose), less than 0.0002% (average 188ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Metabolism: 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 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 50mg 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 Cmax 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 Cmax (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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, Maize starch, Anhydrous calcium hyfdrogen phosphate, Methyl paraben, Propyl paraben, Povidone, Croscarmellose sodium, Magnesium stearate, Purified talc, Sodium starch glycolate, Colloidal anhydrous silica, Wincoat-WT-01215, Isopropyl alcohol, Dichloromethane.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in dry place, below 30°C. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

4 tablets in a Aluminium blisters

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Bliss GVS Pharma Ltd.102, Hyde Park, Saki Vihar Road, Andheri (E), Mumbai – 400072, INDIA.