National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MAN-G (Sildenafil Tablets 100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Sildenafil Citrate BP
Eq. to Sildenafil 100mg
Excipients q.s.
Colour: Brilliant Blue FCF

Excipients:
Microcrystalline cellulose
Calcium Hydrogen Phosphate (Anhydrous)
Hydroxy Propyl Cellulose
Isopropyl Alcohol
Magnesium Stearate
Purified Talcum
Colloidal Silicon Dioxide
Cross Carmellose Sodium
Isopropyl Alcohol
Methylene Chloride
Col Brilient Blue

3. PHARMACEUTICAL FORM:

TABLET

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MAN-G is indicated for the treatment of erectile dysfunction.

4.2 Posology and method of administration

The dose of sildenafil Citrate (**MAN-G**) will be different for different patients. Follow your doctor's orders or the directions on the label. The following information includes only the average doses of sildenafil. If your dose is different, do not change it unless your doctor tells you to do so.
For oral dosage form (tablets):
For treatment of erectile dysfunction:
Adults up to 65 years of age—50 mg as a single dose no more than once a day, 1 hour before sexual intercourse. Alternatively, the medicine may be taken 30 minutes to 4 hours before

sexual intercourse. If needed, your doctor may increase your daily dose to 100 mg or decrease your daily dose to 25 mg.
Adults 65 years of age and older—25 mg as a single dose no more than once a day, 1 hour before sexual intercourse. Alternatively, the medicine may be taken 30 minutes to 4 hoursbefore sexual intercourse. If needed, your doctor may increase your daily dose.
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4.3 Contraindications

Consistent with its known effects on the nitric oxide/cGMP pathway, **MAN-G** was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.
After patients have taken **MAN-G**, it is unknown when nitrates, if necessary, can be safely administered. Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post dose are approximately 2 ng/mL (compared to peak plasma levels of approximately 440 ng/mL) In the following patients: age >65, hepatic impairment (e.g., cirrhosis), severe renal impairment (e.g., creatinine clearance <30 mL/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely coadministered at this time point.
MAN-G is contraindicated in patients with a known hypersensitivity to any component of the tablet.

4.4 Special warnings and precautions for use

There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including **MAN-G**, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

MAN-G has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mmHg). While this normally would be expected to be of little consequence in most patients, prior to prescribing

MAN-G, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.
There is no controlled clinical data on the safety or efficacy of **MAN-G** in the following groups; if prescribed, this should be done with caution.

MAN-G (Sildenafil Tablets 100mg)
Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
Patients with resting hypotension (BP <90/50) or hypertension (BP >170/110);
Patients with cardiac failure or coronary artery disease causing unstable angina;
Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).
Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours

in duration) have been reported infrequently since market approval of **MAN-G**. 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.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant administration of the protease inhibitor ritonavir substantially increases serum concentrations of sildenafil (**11-fold increase in AUC**). If **MAN-G** is prescribed to patients taking ritonavir, caution should be used. Data from subjects exposed to high systemic levels of sildenafil are limited. Visual disturbances occurred more commonly at higher levels of sildenafil exposure. Decreased blood pressure, syncope, and prolonged erection were reported in some healthy volunteers exposed to high doses of sildenafil (200-800 mg). To decrease the chance of adverse events in patients taking ritonavir, a decrease in sildenafil dosage is recommended.
A reduction in Sildenafil clearance occurs when it is coadministered with specific CYP 3A4 inhibitors such as ketoconazole, erythromycin, or itraconazole and with non-specific CYP inhibitors such as cimetidine. It can be expected that concomitant administration of CYP 3A4 inducers, such as rifampicin, will decrease the plasma levels of Sildenafil.

4.6 Pregnancy and lactation

Pregnancy

MAN-G is not indicated for use in newborns, children, or women.
No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the MRHD on a mg/m^2 basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the non-pregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well-controlled studies of sildenafil in pregnant women.

4.7 Effects on ability to drive and use machines

MAN-G may cause drowsiness; patients so affected should not drive or operate machinery.

4.8 Undesirable effects

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.
Less common
Abnormal vision, including blurred vision, seeing shades of colors differently than before, or sensitivity to light; bladder pain; cloudy or bloody urine; dizziness; increased frequency of urination; pain on urination.

Rare
Bleeding of the eye; convulsions (seizures); decreased vision or other changes in vision; double vision; prolonged, painful, or inappropriate erection of penis; redness, burning, or swelling of the eye; vision loss, temporary

Note: The following rare side effects have not been completely established as being caused by sildenafil

Blood sugar problems (more likely with patients with diabetes mellitus), such as anxiety, behavior change similar to drunkenness, blurred vision, cold sweats, confusion, cool and pale skin, difficulty in concentrating, drowsiness, excessive hunger, fast heartbeat, headache, nausea, nervousness, nightmares, restless sleep, shakiness, slurred speech, and unusual tiredness or weakness; bone pain; breast enlargement; chest pain; chills; confusion; convulsions (seizures); deafness; decrease in amount of urine or in frequency of urination; dizziness or lightheadedness, especially when getting up from a lying or sitting position; dry eyes; dry mouth; dryness, redness, scaling, or peeling of the skin; eye pain; fainting or faintness; fast, irregular, or pounding heartbeat; feeling of something in the eye; groups of skin lesions with swelling; headache (severe or continuing); heart failure; hives; increase in size of pupil; increased sweating; increased thirst; itching of skin; low blood pressure; lower back or side pain; migraine headache; nausea (severe or continuing); nervousness; numbness of hands; painful, swollen joints; redness, itching, or tearing of eyes; shortness of breath or troubled breathing; skin paleness; skin rash; skin ulcers; sore throat and fever or chills; sudden weakness; swelling of face, hands, feet, or lower legs; twitching of muscles; unusual tiredness or weakness; unusual feeling of burning or stinging of skin

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. However, check with your doctor if any of the following side effects continue or are bothersome:

More common
Flushing; headache; nasal congestion; stomach discomfort following meals

Less common
Diarrhea

Rare
Anxiety
Note: The following rare side effects have not been completely established as being caused by sildenafil

Abdominal pain; abnormal dreams; aches or pains of muscles; clumsiness or unsteadiness; cough; diarrhea or stomach cramps (severe or continuing); difficulty in swallowing; ear pain; increased amount of saliva; increased skin sensitivity; lack of coordination; loss of bladder control; mental depression; nausea; numbness or tingling of hands, legs, or feet; rectal bleeding; redness or irritation of the tongue; redness, soreness, swelling, or bleeding of gums; ringing or buzzing in ears; sensation of motion, usually whirling, either of one's self or of one's surroundings; sexual problems in men (continuing), including failure to experience a sexual orgasm; sleepiness; sores in mouth and on lips; tense muscles; tightness of chest or wheezing; trembling and shaking; trouble in sleeping; vomiting; waking to urinate at night; worsening of asthma
Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

4.9 Overdose

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 it is not eliminated in the urine.

5. Pharmacological properties

5.1 Pharmacodynamic properties

PHARMACODYNAMIC

Effects of Sildenafil Citrate on Erectile Response: In eight double-blind, placebocontrolled crossover studies of patients with either organic or psychogenic erectile dysfunction, sexual stimulation resulted in improved erections, as assessed by an objective measurement of hardness and duration of erections , after **Sildenafil Citrate** administration compared with placebo. Most studies assessed the efficacy of **Sildenafil Citrate** approximately 60 minutes post dose. The erectile response, as assessed by generally increased with increasing sildenafil dose and plasma concentration. The time course of effect was examined in one study, showing an effect for up to 4 hours but the response was diminished compared to 2 hours.

Effects of Sildenafil Citrate on Blood Pressure: Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease of 8.4/5.5 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different than placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg of **Sildenafil Citrate**, therefore the effects are not related to dose or plasma levels. Larger effects were recorded among patients receiving concomitant nitrates.

Effects of Sildenafil Citrate on Cardiac Parameters: Single oral doses of sildenafil up to 100 mg produced no clinically relevant changes in the ECGs of normal male volunteers

Studies have produced relevant data on the effects of **Sildenafil Citrate** on cardiac output. In one small, open-label, uncontrolled, pilot study, eight patients with stable ischemic heart disease underwent Swan-Ganz catheterization. A total dose of 40 mg sildenafil was administered by four intravenous infusions.
The results from this pilot study are shown in Table 1; the mean resting systolic and diastolic blood pressures decreased by 7% and 10% compared to baseline in these patients. Mean resting values for right atrial pressure, pulmonary artery pressure, pulmonary artery occluded pressure and cardiac output decreased by 28%, 28%, 20% and 7% respectively. Even though this total dosage produced plasma sildenafil concentrations which were approximately 2 to 5 times higher than the mean maximum plasma concentrations following a single oral dose of 100 mg in healthy male volunteers, the hemodynamic response to exercise was preserved in these patients.

Effects of Sildenafil Citrate on Vision: At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended

dose revealed no effects of **Sildenafil Citrate** on visual acuity, electroretinograms, intraocular pressure, or pupillometry.

5.2 Pharmacokinetic properties

Sildenafil Citrate is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. Its pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil. The concomitant use of potent cytochrome P450 3A4 inhibitors (e.g., erythromycin, ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil. Both sildenafil and the metabolite have terminal half lives of about 4 hours.

Mean sildenafil plasma concentrations measured after the administration of a single oral dose of 100 mg to healthy male volunteers is depicted below:

Absorption and Distribution:Sildenafil Citrate is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in in the fasted state. When **Sildenafil Citrate** is taken with a high fat meal, 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%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.
Based upon measurements of sildenafil in semen of healthy volunteers 90 minutes after dosing, less than 0.001% of the administered dose may appear in the semen of patients.

Metabolism and Excretion: Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil. s pharmacologic effects.
After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose). Similar values for pharmacokinetic parameters were seen in normal volunteers and in the patient population, using a population pharmacokinetic approach.

Pharmacokinetics in Special Populations
Geriatrics: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).
Renal Insufficiency: In volunteers with mild (CLcr=50-80 mL/min) and moderate (CLcr=30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of **Sildenafil Citrate** (100 mg) were not altered. In volunteers with severe (CLcr=<30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of

AUC and C_{max} compared to age-matched volunteers with no renal impairment.
Hepatic Insufficiency: In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment.
Therefore, age >65, hepatic impairment and severe renal impairment are associated with increased plasma levels of sildenafil. A starting oral dose of 25 mg should be considered in those patients.

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

Microcrystalline cellulose
Calcium Hydrogen Phosphate (Anhydrous)
Hydroxy Propyl Cellulose
Isopropyl Alcohol
Magnesium Stearate
Purified Talcum
Colloidal Silicon Dioxide
Cross Carmellose Sodium
Isopropyl Alcohol
Methylene Chloride
Col Brilliant Blue

6.2 Incompatibilities
None reported.

6.3 Shelf life
36 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30^{o}C in a cool and dry place, Protect from Light.
Keep out of reach of children.

6.5 Nature and contents of container
Blister of 4 Tablets packed in a printed carton with leaflet inside

6.6 Special precautions for disposal and other handling

No special requirements

7. Manufactured by

LESANTO LABORATORIES
Plot no 9,10,11 & 20 , Survey No. 53
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