MAXEFIL TABLET

DESCRIPTION:

MAXEFIL 100MG TABLET: A blue coloured diamond shaped film coated tablet with score on one side

MAXEFIL 50MG TABLET: A blue coloured diamond shaped film coated tablet with score on one side

COMPOSITION: Each film coated tablet contains 50 or 100mg Sildenafil (as the citrate salt).

PHARMACODYNAMIC: Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)- specific phosphodiesterase type 5 (PDE5). It is used as an oral therapy for erectile dysfunction. The mechanism of erection involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric Oxide activates the enzymes guanylate cyclase. This will result in increased levels of cGMP which produces smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil enhances the effect of nitric oxide by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood to the corpus cavernosum. It has no effect in the absence of sexual stimulation.

PHARMACOKINETICS: *Absorption*: Sildenafil is rapidly absorbed after oral administration. Nonetheless, only about 40% of a dose reaches systemic circulation unchanged. Within 30 – 120 minutes peak plasma concentration usually will be attained. High fat meals delays GI absorption, peak plasma concentrations are reduced by about 30% and time to peak plasma concentration delayed about 60min. *Distribution*: N-desmethyl metabolite and Sildenafil are bound to plasma proteins. Protein binding is independent of total drug concentration. *Metabolism*: It undergoes extensive metabolism in GI mucosa during absorption and on first pass through liver. Sildenafil is metabolized in the liver principally by CYP3A4 and to lesser extent by CYP2C9.The major circulating metabolites results from N-demethylation of sildenafil, and itself further metabolized.
Elimination: Sildenafil is excreted as metabolites mainly in the faeces and to lesser extend in the urine. Terminal elimination half life is about 4 hours.

INDICATIONS: Sildenafil is indicated for the treatment of 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.

DOSAGE & ADMINISTRATION:

Adults

For most patients, the recommended dose is 50mg taken, as needed approximately 1 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100mg or decreased to 25mg. The maximum recommended daily dose is 100mg. The maximum recommended dosing frequency is once per day.

Use in patients with impaired renal function

Dosage adjustments are not required in 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.

Use in patients with impaired hepatic function

Since sildenafil clearance is reduced in patients with hepatic impairement (e.g. cirrhosis), a 25 mg dose should be considered.

Use in patients using other medications
Given the extent of the interaction with patients receiving concomitant therapy with ritonavir. It is recommended not to exceed a maximum single dose of 25mg of sildenafil in a 48-hour period. A starting dose of 25mg should be considered in patients receiving concomitant treatment with CYP 3A4 inhibitors (e.g. erythromycin, saquinavir, ketoconazole, itraconazole). In order to minimize the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating treatment. In addition, initiation of sildenafil at lower doses should be considered.
Use in children
Sildenafil is not indicated for use in children (<18 years old).
Use in elderly men
Dosage adjustments are not required in elderly patients.

ROUTE OF ADMINISTRATION:
Oral administration

CONTRAINDICATIONS:
1. Hypersensitivity to any component of the tablet.
2. 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 contraindicated.
3. Sildenafil should not be used in men for whom sexual activity is inadvisable (i.e patients with unstable angina or severe cardiac failure).
4. Sildenafil is also contraindicated in the patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION).

SIDE EFFECTS:
Immune System disorders
Hypersensitivity reactions (including skin rash)
Gastrointestinal disorders
Dyspepsia, vomiting
Respiratory, thoracic and mediastinal disorders
Rhinitis (nasal congestions)
Nervous System disorders
Seizure, seizure recurrence, headache, dizziness
Cardiac Disorders
Tachycardia
Vascular disorders
Vasodilation (flushing), hypotension, syncope, epistaxis.
Eye disorders
Abnormal vision (blurred vision, increased sensitivity to light), Chromatopsia (mild and transient, predominantly color tinge to vision), eye pain, red eyes/bloodshot eyes.
Reproductive system and Breast disorders
Prolonged erection and/or priapism.

WARNING AND PRECAUTIONS:
Cardiovascular status of patients should be determined first before initiating treatment with sildenafil because there is cardiac risk associated with sexual activity. Sildenafil has the vasodilator properties resulting in mild and transient decrease in blood pressure. Therefore, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilator effects especially in combination with sexual activity prior to prescribing sildenafil. Patients with left ventricular outflow obstruction (e.g. aortic stenosis, idiopathic hypertrophic

subaortic stenosis) or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure can be particularly sensitive to the actions of vasodilators. Prolonged erection greater than 4 hours and priapism (painful erection greater than 6 hours in duration) can damage penile tissue and permanent loss of potency if priapism is not treated. In addition, sildenafil is not indicated for use by women. Sildenafil should be used with caution in patients with anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions which may predispose to priapism (e.g. sickle cell anemia, multiple myeloma or leukemia). Visual defects and cases of NAION can be caused by intake of sildenafil or other PDE5 inhibitors. The patients should be advised that in case of sudden visual loss, to stop taking sildenafil and consult a physician immediately.

PREGNANCY & LACTATION: There are no adequate and well controlled data in pregnant women or lactating women. Sildenafil is not indicated for use in women.

DRUG INTERACTION: Use of sildenafil with drugs that inhibit the cytochrome P450 isoenzymes CYP3A4, such as cimetidine, erythromycin, itraconazole, ketoconazole, and HIV-protease inhibitors, may reduce sildenafil clearance necessitating a reduction in dosage. Co-administration of sildenafil with ritonavir is not advised and in any event the maximum dose of sildenafil should not exceed 25mg within 48 hours. Grape fruit juice should be avoided with sildenafil or other phosphodiesterase type-5 inhibitor as it may increase their plasma concentration.

OVERDOSAGE & TREATMENT: Symptoms of adverse reactions such as headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision are increased. Treatment of overdose requires a standard supportive measure. Since sildenafil is highly bound to plasma proteins and not eliminated in the urine thus renal dialysis is not expected to accelerate clearance.

PRESENTATION: 2 or 4 tablets per blister. 1 blister perbox.

STORAGE: Store below 30^{o}C

MANUFACTURED BY:
Noripharma Sdn. Bhd. (792633-A)
Lot 5030 Jalan Teratai,
5 $^{1}/_{2}$ Mile off Jalan Meru,
41050 Klang,
Selangor Darul Ehsan, Malaysia.

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