For the use only of a Registered medical practitioner, Hospital or Laboratory

Dapoxetine and Vardenafil Tablets

Savitra-Max

COMPOSITION:

Each film coated tablet contains:

Dapoxetine Hydrochloride IP equivalent to Dapoxetine	60 mg
Vardenafil Hydrochloride equivalent to Vardenafil	20 mg
Excipients	q.s.

Colours: Titanium Dioxide BP, Ponceau 4R, Erythrosine

CHEMISTRY

Vardenafil: 4-[2-Ethoxy-5-(4-ethylpiperazin-1-yl)sulfonyl-phenyl]-9-methyl-7- propyl-3,5,6,8-tetrazabicyclo [4.3.0]nona-3,7,9-trien-2-one

Dapoxetine: (+)-(S)-N, N-dimethyl-(‹)-[2-(1-naphthalenyloxy) ethyl]-benzenemethanamine hydrochloride

CATEGORY

Vardenafil: Selective phosphodiesterase type-5 (PDE5) inhibitor

Dapoxetine: Selective serotonin reuptake inhibitor (SSRI)

DESCRIPTION: SAVITRA-MAX contains Vardenafil hydrochloride 20 mg and Dapoxetine hydrochloride 60 mg.

PHARMACOLOGY

Pharmacodynamics

Vardenafil: Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme guanylate cyclase resulting in increased synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP in turn triggers smooth muscle relaxation, allowing increased blood flow into the penis, resulting in erection. The tissue concentration of cGMP is regulated by both the rates of synthesis and degradation via phosphodiesterases (PDEs). The most abundant PDE in the human corpus cavernosum is the cGMP-specific phosphodiesterase type 5 (PDE5); therefore, the inhibition of PDE5 enhances erectile function by increasing the amount of cGMP. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has no effect in the absence of sexual stimulation.

Dapoxetine: The mechanism of action of dapoxetine in premature ejaculation is presumed to be linked to the inhibition of neuronal reuptake of serotonin and the subsequent potentiation of the

neurotransmitter's action at pre- and post-synaptic receptors. Human ejaculation is primarily mediated by the sympathetic nervous system. The ejaculatory pathway originates from a spinal reflex centre, mediated by the brain stem, which is influenced initially by a number of nuclei in the brain (medial preoptic and paraventricular nuclei).

Pharmacokinetics

Vardenafil: Vardenafil is rapidly absorbed with absolute bioavailability of approximately 15%. High-fat meals caused a reduction in C_{max} by 18-50%.

Vardenafil and its major circulating metabolite are highly bound to plasma proteins (about 95%). This protein binding is reversible and independent of total drug concentrations.
Vardenafil is metabolized predominantly by the hepatic enzyme CYP3A4, with contribution from the CYP3A5 and CYP2C isoforms.
The terminal half-life of vardenafil and its primary metabolite (M1) is approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the feces (approximately 91-95% of administered oral dose) and to a lesser extent in the urine (approximately 2-6% of administered oral dose).

Dapoxetine: Dapoxetine is rapidly absorbed with maximum plasma concentrations (C_{max}) occurring approximately 1-2 hours after tablet intake. The absolute bioavailability is 42% (range 15- 76%). Ingestion of a high fat meal modestly reduced the C_{max} (by 10%) and modestly increased the AUC (by 12%) of dapoxetine and slightly delayed the time for dapoxetine to reach peak concentrations; however, the extent of absorption was not affected by consumption of a high fat meal.
Greater than 99% of dapoxetine is bound *in vitro* to human proteins. The active metabolite desmethyldapoxetine is 98.5% protein bound.
Dapoxetine was extensively metabolized to multiple metabolites primarily through the following biotransformational pathways: N-oxidation, N-demethylation, naphthyl hydroxylation, glucuronidation and sulfation.
The terminal half-life is approximately 19 hours following oral administration.

INDICATIONS

SAVITRA-MAX is indicated for the treatment of Erectile Dysfunction (ED) and Premature Ejaculation (PE) in men.

DOSAGE AND ADMINISTRATION

Take 1 tablet of SAVITRA-MAX before 1-3 hours of sexual activity. The maximum recommended dosing frequency is once daily.

CONTRAINDICATIONS

SAVITRA-MAX is contraindicated in patients with known hypersensitivity, moderate and severe hepatic impairment, significant pathological cardiac conditions (such as heart failure (NYHA class II-IV), conduction abnormalities (second- or third-degree AV block or sick sinus syndrome), ischemic heart disease or valvular disease.

WARNINGS AND PRECAUTIONS

SAVITRA-MAX is prescribed for adult males only (18 years and older).
SAVITRA-MAX is indicated in men with premature ejaculation (PE) and erectile dysfunction (ED).
SAVITRA-MAX must not be used by anyone taking nitrate medication or alcohol.
Use of SAVITRA-MAX is not recommended for people with a history of cardiovascular disease, renal impairment, hepatic impairment and urological conditions.
Consult a medical professional immediately if you experience erections lasting longer than 4 hours and priapism (prolonged erections greater than 6 hours).
Patients should be advised not to use SAVITRA-MAX in combination with recreational drugs such as ketamine, methylenedioxy-methamphetamine (MDMA) and lysergic acid diethylamide (LSD) may lead to potentially serious reactions if combined with SAVITRA-MAX.
The occurrence of syncope and possibly prodromal symptoms appears dose dependent as demonstrated by higher incidence among patients treated with doses of Dapoxetine higher than 60 mg, the recommended maximum daily dose.
SAVITRA-MAX should be prescribed with caution in patients taking medicinal products with vasodilatation properties (such as alpha adrenergic receptor antagonists, nitrates, PDE5 inhibitors) due to possible reduced orthostatic tolerance.
SAVITRA-MAX should not be used in patients with a history of mania/hypomania or bipolar disorder and should be discontinued in any patient who develops symptoms of these disorders.
SAVITRA-MAX should be discontinued in any patient who develops seizures and avoided in patients with unstable epilepsy. Patients with controlled epilepsy should be carefully monitored.

DRUG INTERACTIONS

SAVITRA-MAX is contraindicated for concomitant treatment with monoamine oxidase inhibitors (MAOIs), thioridazine, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), L-tryptophan, triptans, tramadol, linezolid, lithium, St. John's Wort (Hypericum perforatum), nitrates, alpha-blockers, antihypertensive, antacids (magnesium-aluminum hydroxide, ranitidine, cimetidine), glyburide, P-glycoprotein (digoxin), aspirin, nifedipine and warfarin,.
SAVITRA-MAX is contraindicated for concomitant treatment with potent cytochrome P450 inhibitors such as ketoconazole, itraconazole, indinavir, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir, atazanavir, erythromycin, clarithromycin, fluconazole, amprenavir, fosamprenavir, aprepitant, verapamil, diltiazem, desmipramine and midazolam.

USE IN PREGNANCY AND LACTATION

SAVITRA-MAX is not safe for use during pregnancy and lactation.

ADVERSE REACTIONS

According to reported studies, most common adverse drug reactions are headache, dizziness, nausea, diarrhea, insomnia, fatigue, flushing, nasal congestion, dyspepsia, sinusitis, flu syndrome, increased creatine kinase and back pain.

Other reported adverse reactions include increased blood pressure, tremor, paraesthesia, disturbance in attention, blurred vision, tinnitus, sinus congestion, yawning, abdominal pain, dry mouth, vomiting, flatulence, hyperhidrosis, irritability, erectile dysfunction, anxiety, nervousness, decreased libido, depression, apathy and abnormal dreams.

OVERDOSAGE

In general, symptoms of overdose with SSRIs include serotonin-mediated adverse reactions such as somnolence, gastrointestinal disturbances such as nausea and vomiting, tachycardia, tremor, agitation and dizziness.

In cases of overdose, standard supportive measures should be adopted as required. Due to high protein binding and large volume of distribution, forced diuresis, renal dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

PRESENTATION : Blister of 4 Tablets

STORAGE: Store in a cool and dry place below 30°C.
Protect from light and moisture.

Keep out of reach of children.

LAST UPDATE: October 2014.

Manufactured by:
SAVA HEALTHCARE LIMITED
507-B to 512, G.I.D.C. Estate,
Wadhwan City-363035,
Surendranagar, Gujarat. INDIA.
www.savaglobal.com

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