Bosch

For Medical Professional only

Symbal Capsules
(Duloxetine)

(Product Specs.: U.S.P.)

سمبل کیپسولز

DESCRIPTION:
Symbal (duloxetine) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropyl-amine hydrochloride. The empirical formula is $C_{18}H_{19}NOS \cdot HCL$, which corresponds to a molecular weight of 333.88.

Composition
Each capsule contains: Duloxetine HCl U.S.P. eq. to Duloxetine..... 20mg (As enteric coated pellets).
(Product Specs.: U.S.P.)
Each capsule contains: Duloxetine HCl U.S.P. eq. to Duloxetine..... 30mg (As enteric coated pellets).
(Product Specs.: U.S.P.)
Each capsule contains: Duloxetine HCl U.S.P. eq. to Duloxetine..... 60mg (As enteric coated pellets).
(Product Specs.: U.S.P.)

CLINICAL PHARMACOLOGY:
Mechanism of action:
Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

PHARMACOKINETIC PROPERTIES:
Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation.

Absorption
Duloxetine is well absorbed after oral administration, with a Cmax occurring 6 hours post-dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%).

Distribution
Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha1-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation
Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites, glucuronide conjugate of 4-hydroxy duloxetine and sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine.

Elimination
The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Specific Populations
Hepatic Impairment
Hepatic impairment: Moderate liver disease (Child-Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3-times longer, and the AUC was 3.7-times higher in patients with moderate liver disease.

Pediatrics
Pharmacokinetics of duloxetine in paediatric patients aged 7 to 17 years with major depressive disorder following oral administration of 20 to 120 mg once daily dosing regimen was characterized using population modelling analyses. The model-predicted duloxetine steady-state plasma concentrations in paediatric patients were mostly within the concentration range observed in adult patients.

Age
Pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly.

THERAPEUTIC INDICATIONS:
- Treatment of major depressive disorder.
- Treatment of generalised anxiety disorder.
- Management of neuropathic pain associated with diabetic peripheral neuropathy.
- Management of fibromyalgia.
- Management of chronic musculoskeletal pain.

DOSAGE AND ADMINISTRATION:
Symbal (Duloxetine) should be swallowed whole and should not be

chewed or crushed, nor should the capsule be opened and its contents sprinkled on food or mixed with liquids. All of these might affect the enteric coating. Symbal (Duloxetine) should be given without regard to meals.

Major Depressive Disorder: Symbal (Duloxetine) should be administered at a total dose of 40 mg/day (given as 20 mg twice daily) to 60 mg/day (given either once daily or as 30 mg twice daily). For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer any additional benefits. The safety of doses above 120 mg/day has not been adequately evaluated.

Generalized Anxiety Disorder: For most patients, the recommended starting dose for Symbal (Duloxetine) is 60 mg administered once daily. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg once daily dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit. Nevertheless, if a decision is made to increase the dose beyond 60 mg once daily, dose increases should be in increments of 30 mg once daily. The safety of doses above 120 mg once daily has not been adequately evaluated.

Diabetic Peripheral Neuropathic Pain: The recommended dose for Symbal (Duloxetine) is 60 mg administered once daily. There is no evidence that doses higher than 60 mg confer additional significant benefit and the higher dose is clearly less well tolerated. For patients for whom tolerability is a concern, a lower starting dose may be considered.

Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment.

Fibromyalgia: The recommended dose for Symbal (Duloxetine) is 60 mg administered once daily. Treatment should begin at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. Some patients may respond to the starting dose. There is no evidence that doses greater than 60 mg/day confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions.

Chronic Musculoskeletal Pain: The recommended dose for Symbal (Duloxetine) is 60 mg once daily. Dosing may be started at 30 mg for one week, to allow patients to adjust to the medication before increasing to 60 mg once daily. There is no evidence that higher doses confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions.

Specific Polpulation
Hepatic Impairment
Symbal (Duloxetine) must not be used in patients with liver disease resulting in hepatic impairment.

Renal Impairment
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). Symbal (Duloxetine) must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min).

Paediatric population
Duloxetine should not be used in children and adolescents under the age of 18 years for the treatment of major depressive disorder because of safety and efficacy concerns.

The safety and efficacy of duloxetine for the treatment of generalised anxiety disorder in paediatric patients aged 7-17 years have not been established.

Discontinuation of Treatment
Abrupt discontinuation should be avoided. When stopping treatment with Symbal (Duloxetine) the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients.
Concomitant use of Symbal (Duloxetine) with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated.
Liver disease resulting in hepatic impairment.
Symbal (Duloxetine) should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e. potent CYP1A2 inhibitors) since the combination results in elevated plasma concentrations of duloxetine.
Severe renal impairment (creatinine clearance <30 ml/min).
The initiation of treatment with Symbal (Duloxetine) is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS:
Mania and Seizures
Symbal (Duloxetine) should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Mydriasis
Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing Symbal (Duloxetine) to patients with increased intraocular pressure or those at risk of acute narrow-angle glaucoma.

Blood Pressure and Heart Rate
Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism. For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered. In patients with uncontrolled hypertension duloxetine should not be initiated.

Serotonin syndrome
As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with duloxetine treatment, particularly with concomitant use of other serotonergic agents , with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability, neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

St John's Wort
Adverse reactions may be more common during concomitant use of Symbal (Duloxetine) and herbal preparations containing St John's Wort (Hypericum perforatum).

Suicide
Major Depressive Disorder and Generalised Anxiety Disorder: Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide (suicide-related events). As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment.

Diabetic Peripheral Neuropathic Pain: As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation.

Use in Children and Adolescents Under 18 Years of Age
Symbal (Duloxetine) should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, and anger).

Haemorrhage
Duloxetine may increase the risk of postpartum haemorrhage. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g., NSAIDs or acetylsalicylic acid (ASA)), and in patients with known bleeding tendencies.

Hyponatraemia
Hyponatraemia has been reported when administering Symbal, including cases with serum sodium lower than 110 mmol/l. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients, or patients treated with diuretics.

Akathisia/Psychomotor Restlessness
The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hepatitis/Increased Liver Enzymes
Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis, and jaundice have been reported with duloxetine . Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

Sucrose
Symbal (Duloxetine) hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

DRUG INTERACTIONS:
Monoamine Oxidase Inhibitors (MAOIs): Due to the risk of serotonin syndrome, duloxetine should not be used in combination with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping Symbal before starting an MAOI.

The concomitant use of Symbal with selective, reversible MAOIs, like moclobemide, is not recommended. The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with Symbal.

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUCo-t 6-fold. Therefore, Symbal should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine.

CNS Medicinal Products: The risk of using duloxetine in combination with other CNS-active medicinal products has not been systematically evaluated, except in the cases described in this section.

Serotonergic agents: Caution is advisable if Symbal (Duloxetine) is used concomitantly with serotonergic agents, MAOIs like moclobemide or linezolid, St John's Wort (Hypericum perforatum) or triptans, tramadol, pethidine, and tryptophan.

Effect of Duloxetine on Other Medicinal Products
Medicinal products metabolised by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. Caution is advised if Symbal (Duloxetine) is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), particularly if they have a narrow therapeutic index (such as flecainide, propafenone, and metoprolol).

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction.

Effects of Other Medicinal Products on Duloxetine
Antacids and H2 antagonists: Co-administration of duloxetine with aluminium- and magnesium-containing antacids, or duloxetine with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

PREGNANCY:
There are no adequate data on the use of duloxetine in pregnant women. Duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

LACTATION:
The safety of duloxetine in infants is not known, the use of duloxetine while breast-feeding is not recommended.

ADVERSE EFFECTS:
Common: Decreased appetite, Insomnia Agitation, Libido decreased, Anxiety, Orgasm abnormal, Abnormal dreams, Dizziness, Lethargy, Tremor, Paraesthesia , Blurred vision, Tinnitus, Palpitations, Blood pressure increase, Flushing, Yawning, Constipation, Diarrhoea, Abdominal pain, Vomiting. Dyspepsia, Flatulence, Sweating increased, Rash, Musculoskeletal pain, Muscle spasm, Dysuria Pollakiuria, Erectile dysfunction, Ejaculation disorder, Ejaculation delayed, Fatigue, Weight decrease.

Uncommon: Laryngitis, Hyperglycaemia, Suicidal ideation, Sleep disorder, Bruxism, Disorientation, Apathy, Myoclonus, Akathisia, Nervousness, Disturbance in attention, Dysgeusia, Dyskinesia, Restless legs syndrome, Poor quality sleep, Mydriasis, Visual impairment, Vertigo, Ear pain, Tachycardia Supraventricular arrhythmia, mainly atrial fibrillation, Syncope, Hypertension, Orthostatic hypotension, Peripheral coldness, Gastrointestinal haemorrhage, Gastroenteritis, Eructation, Gastritis, Dysphagia, Elevated liver enzymes (ALT, AST, alkaline phosphatase), Acute liver injury, Night sweats Urticaria Dermatitis contact, Cold sweat, Photosensitivity reactions, Increased tendency to bruise, Muscle tightness Muscle twitching, Urinary retention, Urinary hesitation, Nocturia, Polyuria, Urine flow decreased, Gynaecological haemorrhage, Menstrual disorder, Sexual dysfunction, Testicular pain, Chest pain, Feeling abnormal, Feeling cold, Thirst, Chills, Malaise, Feeling hot, Gait disturbance, Weight increase, Blood creatine phosphokinase increased, Blood potassium increased.

Rare: Anaphylactic reaction, Hypersensitivity disorder, Hypothyroidism, Dehydration, Hyponatraemia, SIADH, Suicidal, behavior, Mania, Hallucinations, Aggression and anger, Serotonin syndrome, Convulsion, Psychomotor restlessness, Extra-pyramidal symptoms, Glaucoma, Interstitial lung disease, Eosinophilic pneumonia, Stomatitis, Haematochezia, Breath odour, Microscopic colitis, Hepatic failure, Jaundice, Stevens-Johnson Syndrome, Angioneurotic oedema, Trismus, Menopausal symptoms Galactorrhoea, Hyperprolactinaemia , Postpartum haemorrhage, Blood cholesterol increased.

Very Rare: Cutaneous vasculitis

OVER DOSAGE:
There is no specific antidote to duloxetine. In the treatment of overdosage, oral activated charcoal should be considered if more than 7.5mg/kg of duloxetine has been ingested and the patient presents within 1 hour of ingestion; this should be followed by symptomatic and supportive therapy. Dialysis, hemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Presentation
Symbal 20mg Capsule: Cold Form & Cold Seal Pack of 14 Capsules.
Symbal 30mg Capsule: Cold Form & Cold Seal Pack of 10 Capsules.
Symbal 60mg Capsule: Cold Form & Cold Seal Pack of 10 Capsules.

STORAGE AND INSTRUCTIONS:
- Protect from heat, sunlight & moisture, store below 30ºC.
- Keep out of the reach of children.
- The expiration date refer to the product correctly stored at the required condition.
- Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com
- To be sold on prescription of a registered medical practitioner only.

ہدایات :

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
30°C سے کم درجہ حرارت پر دھوپ، گرمی اور نمی سے محفوظ رکھیں۔
بچّوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ میڈیکل پریکٹیشنر کے نسخے پر فروخت کے لئے۔

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