SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HENKA 30 (Duloxetine Delayed Release Capsules USP 30mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Delayed Release Capsule contains Duloxetine Hydrochloride equivalent to Duloxetine USP 30mg

3. PHARMACEUTICAL FORM

Delayed Release Capsules:

Duloxetine Delayed Release Capsules USP 30mg:

Opaque blue Cap/ Opaque green body size '1' hard gelatin capsule imprinted with 'H' on cap and '192' on body, filled with white to off white colored pellets..

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Duloxetine Capsules are indicated for the treatment of:

- Major depressive disorder in adults
- Generalized anxiety disorder in adults and pediatric patients 7 years of age and older
- Diabetic peripheral neuropathic pain in adults
- Fibromyalgia in adults and pediatric patients 13 years of age and older
- Chronic musculoskeletal pain in adults

4.2 Posology and method of administration

Important Administration Instructions

Administer Duloxetine Capsules orally (with or without meals) and swallow whole. Do not chew or crush, and do not open the delayed-release capsule and sprinkle its contents on food or mix with liquids because these actions might affect the enteric coating. If a dose of Duloxetine Capsule is missed, take the missed dose as soon as it is remembered. If it is almost time for the next dose, skip the missed dose and take the next dose at the regular time. Do not take two doses of Duloxetine Capsules at the same time.

Dosage for Treatment of Major Depressive Disorder in Adults

mg/day dose was shown to be effective, there is no evidence that doses

greater than 30 mg/day confer any additional benefits. Periodically reassess to determine the need for maintenance treatment and the appropriate dosage for such treatment.

Dosage for Treatment of Generalized Anxiety Disorder

Recommended Dosage in Adults Less than 65 Years of Age

For most adults less than 65 years of age with GAD, initiate Duloxetine Capsules30 mg 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 Duloxetine Capsules before increasing to 30 mg once daily. While a 120 mg once daily dosage was shown to be effective, there is no evidence that doses greater than 30 mg/day confer additional benefit. Nevertheless, if a decision is made to increase the dosage beyond 30 mg once daily, increase dosage in increments of 30 mg once daily. Periodically reassess to determine the continued need for maintenance treatment and the appropriate dosage for such treatment.

Recommended Dosage in Geriatric Patients

In geriatric patients with GAD, initiate Duloxetine Capsules at a dosage of 30 mg once daily for 2 weeks before considering an increase to the target dose of 30 mg/day. Thereafter, patients may benefit from doses above 30 mg once daily. If a decision is made to increase the dose beyond 30 mg once daily, increase dose in increments of 30 mg once daily. The maximum dose studied was 120 mg per day.

Recommended Dosage in Pediatric Patients 7 to 17 Years of Age

Initiate Duloxetine Capsules in pediatric patients 7 to 17 years of age with GAD at a dosage of 30 mg once daily for 2 weeks before considering an increase to 30 mg once daily. The recommended dosage range is 30 to 30 mg once daily. Some patients may benefit from dosages above 30 mg once daily. If a decision is made to increase the dose beyond 30 mg once daily, increase dosage in increments of 30 mg once daily. The maximum dose studied was 120 mg per day.

Dosage for Treatment of Diabetic Peripheral Neuropathic Pain in Adults

Administer 30 mg once daily in adults with diabetic peripheral neuropathic pain. There is no evidence that doses higher than 30 mg once daily confer additional significant benefit and the higher dosage 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, consider a lower starting dosage and gradual increase in dosage for patients with renal impairment

Dosage for Treatment of Fibromyalgia

Recommended Dosage in Adults

The recommended Duloxetine Capsules dosage is 30 mg once daily in adults with fibromyalgia. Begin treatment at 30 mg once daily for 1 week, to allow patients to adjust to Duloxetine Capsules before increasing to 30 mg once daily. Some patients may respond to the starting dosage. There is no evidence that dosages greater than 30 mg/day confer additional benefit, even in patients who do not respond to a 30 mg/day dosage, and higher dosages were associated with a higher rate of adverse reactions.

Recommended Dosage in Pediatric Patients 13 to 17 Years of Age

The recommended starting Duloxetine Capsules dosage in pediatric patients 13-17 years of age with fibromyalgia is 30 mg once daily. The dosage may be increased to 30 mg once daily based on response and tolerability.

Dosage for Treatment of Chronic Musculoskeletal Pain in Adults

The recommended Duloxetine Capsules dosage is 30 mg once daily in adults with chronic musculoskeletal pain. Begin treatment at 30 mg once daily for one week, to allow patients to adjust to Duloxetine Capsules before increasing to 30 mg once daily. There is no evidence that higher dosages confer additional benefit, even in patients who do not respond to a 30 mg once daily dosage, and higher dosages are associated with a higher rate of adverse reactions

Dosage in Patients with Hepatic Impairment or Severe Renal Impairment

Avoid use in patients with chronic liver disease or cirrhosis

Avoid use in patients with severe renal impairment, GFR <30 mL/minute

Discontinuing Duloxetine Capsules

Adverse reactions after discontinuation of Duloxetine D.R Capsules, after abrupt or tapered discontinuation, include: dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible

Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with Duloxetine D.R Capsules. Conversely, at least 5 days should be allowed after stopping Duloxetine Capsules before starting an MAOI intended to treat psychiatric disorders

Use of Duloxetine Capsules with Other MAOIs such as Linezolid or Methylene Blue

Do not start Duloxetine Capsules in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered

In some cases, a patient already receiving Duloxetine Capsules therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, Duloxetine Capsules should be stopped promptly, and linezolid or intravenous methylene blue can be administered.

The patient should be monitored for symptoms of serotonin syndrome for 5 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Duloxetine Capsules may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with Duloxetine Capsules is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use

4.3 Contraindications

The use of MAOIs intended to treat psychiatric disorders with Duloxetine Capsules or within 5 days of stopping treatment with Duloxetine Capsules is contraindicated because of an increased risk of serotonin syndrome. The use of Duloxetine Capsules within 14 days of stopping an MAOI intended to treat psychiatric disorders is contraindicated.

Starting Duloxetine Capsules in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome

4.4 Special warnings and special precautions for use

Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short- term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in TABLE 1.

TABLE 1

Age Range	**Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated**
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric Duloxetine Capsules trials. There were suicides in the adult Duloxetine Capsules trials, but the number was not sufficient to reach any conclusion about Duloxetine Capsules effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms for descriptions of the risks of discontinuation of Duloxetine D.R Capsules.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Duloxetine Capsules should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Duloxetine Capsules is not approved for use in treating bipolar depression.

Hepatotoxicity

There have been reports of hepatic failure, sometimes fatal, in patients treated with Duloxetine D.R Capsules. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal (ULN) with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Duloxetine Capsules should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Duloxetine Capsules increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (92/34,756) of Duloxetine Capsules-treated patients. In most patients, the median time to detection of the transaminase elevation was about two months. In adult placebo-controlled trials, for patients with normal and abnormal baseline ALT values, elevation of ALT >3 times the ULN occurred in 1.25% (144/11,496) of Duloxetine Capsules-treated patients compared to 0.45% (39/8716) of placebo-treated patients. In adult placebo-controlled studies using a fixed dose design, there was evidence of a Duloxetine Capsules dose response relationship for ALT and AST elevation of >3 times the ULN and
>5 times the ULN, respectively.

Because it is possible that Duloxetine Capsules and alcohol may interact to cause liver injury or that Duloxetine Capsules may aggravate pre-existing liver disease, Duloxetine Capsules should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Orthostatic Hypotension, Falls and Syncope

Orthostatic hypotension, falls, and syncope have been reported in patients treated with the recommended Duloxetine Capsules dosages. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during Duloxetine Capsules treatment, particularly after dose increases. The risk of falling appears to be related to the degree of orthostatic decrease in blood pressure (BP) as well as other factors that may increase the underlying risk of falls.

In an analysis of patients from all placebo-controlled trials, patients treated with Duloxetine Capsules reported a higher rate of falls compared to patients treated with placebo. Risk appears to be related to the presence of orthostatic decrease in BP. The risk of BP decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors and in patients taking Duloxetine Capsules at doses above 30 mg daily. Consideration should be given to dose reduction or discontinuation of Duloxetine Capsules in patients who experience symptomatic orthostatic hypotension, falls and/or syncope during Duloxetine Capsules therapy.

Risk of falling also appeared to be proportional to a patient's underlying risk for falls and appeared to increase steadily with age. As geriatric patients tend to have a higher underlying risk for falls due to a higher prevalence of risk factors such as use of multiple medications, medical comorbidities and gait disturbances, the impact of increasing age by itself is unclear. Falls with serious consequences including fractures and hospitalizations have been reported with Duloxetine Capsules use

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Duloxetine D.R Capsules, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Duloxetine Capsules with MAOI antidepressants is contraindicated. Duloxetine Capsules should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Duloxetine D.R Capsules. Duloxetine Capsules should be discontinued before initiating treatment with the MAOI

If concomitant use of Duloxetine Capsules with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, amphetamines, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases. Treatment with Duloxetine Capsules and any concomitant serotonergic agents, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including Duloxetine D.R Capsules, may increase the risk of bleeding events. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. A post-marketing study showed a higher incidence of postpartum hemorrhage in mothers taking Duloxetine D.R Capsules. Other bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life- threatening hemorrhages. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anti-coagulants may add to this risk.

Inform patients about the risk of bleeding associated with the concomitant use of Duloxetine Capsules and NSAIDs, aspirin, or other drugs that affect coagulation

Severe Skin Reactions

Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur with Duloxetine D.R Capsules. The reporting rate of SJS associated with Duloxetine Capsules use exceeds the general population background incidence rate for this serious skin reaction (1 to 2 cases per million person years). The reporting rate is generally accepted to be an underestimate due to underreporting.

Duloxetine Capsules should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.

Discontinuation Syndrome

Discontinuation symptoms have been systematically evaluated in patients taking Duloxetine D.R Capsules. Following abrupt or tapered discontinuation in adult placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in Duloxetine Capsules-treated patients compared to those discontinuing from placebo: dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Duloxetine D.R Capsules. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. 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 healthcare provider may continue decreasing the dose but at a more gradual rate

Activation of Mania/Hypomania

In adult placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (4/3779) of Duloxetine Capsules-treated patients and 0.04% (1/2536) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP, GAD, fibromyalgia, or chronic musculoskeletal pain placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Duloxetine Capsules should be used cautiously in patients with a history of mania.

Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including Duloxetine Capsules may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Seizures

Duloxetine Capsules has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In adult placebo-controlled clinical trials, seizures/convulsions occurred in 0.02% (3/12,722) of patients treated with Duloxetine Capsules and 0.01% (1/9513) of patients treated with placebo. Duloxetine Capsules should be prescribed with care in patients with a history of a seizure disorder.

Increases in Blood Pressure

In adult placebo-controlled clinical trials across the approved adult populations from baseline to endpoint, Duloxetine Capsules treatment was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.3 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of Duloxetine Capsules on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily (approximately 3.3 times the maximum recommended dosage). At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment

Clinically Important Drug Interactions

Both CYP1A2 and CYP2D6 are responsible for Duloxetine Capsules metabolism.

Potential for Other Drugs to Affect Duloxetine D.R Capsules

CYP1A2 Inhibitors -Co-administration of Duloxetine Capsules with potent CYP1A2 inhibitors should be avoided.

CYP2D6 Inhibitors — Because CYP2D6 is involved in Duloxetine Capsules metabolism, concomitant use of Duloxetine Capsules with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 30%) of Duloxetine Capsules.

Potential for Duloxetine Capsules to Affect Other Drugs

Drugs Metabolized by CYP2D6 — Co-administration of Duloxetine Capsules with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with

caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Duloxetine D.R Capsules. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Duloxetine Capsules and thioridazine should not be co-administered

Other Clinically Important Drug Interactions

Alcohol — Use of Duloxetine Capsules concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Duloxetine Capsules should not be prescribed for patients with substantial alcohol use

CNS Acting Drugs — Given the primary CNS effects of Duloxetine Capsules, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Duloxetine Capsules. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported with Duloxetine Capsules use and appeared to be reversible when Duloxetine Capsules was discontinued. Geriatric patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of Duloxetine Capsules should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

Use in Patients with Concomitant Illness

Clinical experience with Duloxetine Capsules in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Duloxetine Capsule's enteric coating. In extremely acidic conditions, Duloxetine Capsules, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Duloxetine Capsules in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Duloxetine Capsules has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Impairment

Avoid use in patients with chronic liver disease or cirrhosis.

Severe Renal Impairment

Avoid use in patients with severe renal impairment, GFR <30 mL/minute. Increased plasma concentration of Duloxetine Capsules, and especially of its metabolites, occurred in patients with end-stage renal disease (requiring dialysis).

Glycemic Control in Patients with Diabetes

As observed in DPNP trials, Duloxetine Capsules treatment worsened glycemic control in some patients with diabetes. In three clinical trials of Duloxetine Capsules for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A1c (HbA1c) was 7.8%. In the 12-week acute treatment phase of these studies, Duloxetine Capsules was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Duloxetine Capsules group and decreased by 11.5 mg/dL in the routine care group. HbA1c increased by 0.5% in the Duloxetine Capsules group and by 0.2% in the routine care group.

Urinary Hesitation and Retention

Duloxetine Capsules is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Duloxetine Capsules, consideration should be given to the possibility that they might be drug-related.

In post marketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with Duloxetine Capsules use, hospitalization and/or catheterization has been needed.

4.5 Interaction with other medicinal products and other forms of interaction

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2

When Duloxetine Capsules 30 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the Cmax was increased about 2.5-fold, and duloxetine t1/2 was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin

Inhibitors of CYP2D6

Concomitant use of Duloxetine Capsules (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 30%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine)

Dual Inhibition of CYP1A2 and CYP2D6

Concomitant administration of Duloxetine Capsules 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are co- administered with warfarin. Concomitant administration of warfarin (2-9 mg once daily) under steady state conditions with Duloxetine Capsules 30 or 120 mg once daily for up to 14 days in healthy subjects (n=15) did not significantly change INR from baseline (mean INR changes ranged from 0.05 to +0.07). The total warfarin (protein bound plus free drug) pharmacokinetics ($AUC_{\tau,ss}$, $C_{max,ss}$ or $t_{max,ss}$) for both R- and S-warfarin were not altered by duloxetine. Because of the potential effect of duloxetine on platelets, patients receiving warfarin therapy should be carefully monitored when Duloxetine Capsules is initiated or discontinued

Lorazepam

Under steady-state conditions for Duloxetine Capsules (30 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam

Under steady-state conditions for Duloxetine Capsules (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Drugs that Affect Gastric Acidity

Duloxetine Capsules has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Duloxetine Capsules, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Duloxetine Capsules in patients with conditions that may slow gastric emptying (e.g., some

diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Duloxetine Capsules with aluminum- and magnesium-containing antacids (51 mEq) or Duloxetine Capsules with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption

Drugs Metabolized by CYP1A2

In vitro drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in in vitro studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%- 27%) when co-administered with Duloxetine Capsules (30 mg twice daily).

Drugs Metabolized by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6. When Duloxetine Capsules was administered (at a dose of 30 mg twice daily) in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold

Drugs Metabolized by CYP2C9

Results of in vitro studies demonstrate that duloxetine does not inhibit activity. In a clinical study, the pharmacokinetics of S-warfarin, a CYP2C9 substrate, were not significantly affected by duloxetine

Drugs Metabolized by CYP3A

Results of in vitro studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19

Results of in vitro studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Monoamine Oxidase Inhibitors (MAOIs)

Refer Dosage and Administration, Contraindications and Warnings and Precautions.

Serotonergic Drugs

Refer Dosage and Administration, Contraindications and Warnings and Precautions.

Alcohol

When Duloxetine Capsules and ethanol were administered several hours apart so that peak concentrations of each would coincide, Duloxetine Capsules did not increase the impairment of mental and motor skills caused by alcohol.

In the Duloxetine Capsules clinical trials database, three Duloxetine Capsules -treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen

CNS Drugs

Refer Warnings and Precautions

Drugs Highly Bound to Plasma Protein

Because duloxetine is highly bound to plasma protein, administration of Duloxetine Capsules to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions. However, co-administration of Duloxetine Capsules (30 or 120 mg) with warfarin (2-9 mg), a highly protein-bound drug, did not result in significant changes in INR and in the pharmacokinetics of either total S-or total R-warfarin (protein bound plus free drug).

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors the pregnancy outcomes in women exposed to Duloxetine Capsules during pregnancy.

Risk Summary

Data from a postmarketing retrospective cohort study indicate that use of duloxetine in the month before delivery may be associated with an increased risk of postpartum hemorrhage. Data from published literature and from a postmarketing retrospective cohort study have not identified a clear drug-associated risk of major birth defects or other adverse developmental outcomes. There are risks associated with untreated depression and fibromyalgia in pregnancy, and with exposure to SNRIs and SSRIs, including Duloxetine Capsules, during pregnancy.

In rats and rabbits treated with duloxetine during the period of organogenesis, fetal weights were decreased but there was no evidence of developmental effects at doses up to 3 and 6 times, respectively, the maximum recommended human dose (MRHD) of 120 mg/day given to adolescents on a mg/m2

basis. When duloxetine was administered orally to pregnant rats throughout gestation and lactation, pup weights at birth and pup survival to 1 day postpartum were decreased at a dose 2 times the MRHD given to adolescents on a mg/m2 basis. At this dose, pup behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity were observed. Post-weaning growth was not adversely affected.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Women who discontinue antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continue antidepressants. This finding is from a prospective, longitudinal study that followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Pregnant women with fibromyalgia are at increased risk for adverse maternal and infant outcomes including preterm premature rupture of membranes, preterm birth, small for gestational age, intrauterine growth restriction, placental disruption, and venous thrombosis. It is not known if these adverse maternal and fetal outcomes are a direct result of fibromyalgia or other comorbid factors.

Maternal Adverse Reactions

Use of duloxetine in the month before delivery may be associated with an increased risk of postpartum hemorrhage

Fetal/Neonatal Adverse Reaction

Neonates exposed to Duloxetine Capsules and other SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These findings are consistent with either a direct toxic effect of the SNRIs or SSRIs, or possibly, a drug

discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome.

Data

Human Data

Data from a postmarketing retrospective claims-based cohort study found an increased risk for postpartum hemorrhage among 955 pregnant women exposed to duloxetine in the last month of pregnancy compared to 4,128,430 unexposed pregnant women (adjusted relative risk: 1.53; 95% CI: 1.08-2.18). The same study did not find a clinically meaningful increase in the risk for major birth defects in the comparison of 2532 women exposed to duloxetine in the first trimester of pregnancy to 1,284,827 unexposed women after adjusting for several confounders. Methodologic limitations include possible residual confounding, misclassification of exposure and outcomes, lack of direct measures of disease severity, and lack of information about alcohol use, nutrition, and over-the-counter medication exposures.

Animal Data

In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of malformations or developmental variations at doses up to 45 mg/kg/day [3 and 6 times, respectively, the MRHD of 120 mg/day given to adolescents on a mg/m2 basis]. However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (approximately equal to the MRHD in rats and 2 times the MRHD in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (2 times the MRHD given to adolescents on a mg/m2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

Lactation

Risk Summary

Data from published literature report the presence of duloxetine in human milk. There are reports of sedation, poor feeding, and poor weight gain in infants exposed to duloxetine through breast milk. There are no data on the effect of duloxetine on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Duloxetine Capsules and any potential adverse effects on the breastfed child from Duloxetine Capsules or from the underlying maternal condition.

Clinical Considerations

Infants exposed to Duloxetine Capsules should be monitored for sedation, poor feeding and poor weight gain.

Data

Disposition of Duloxetine Capsules was studied in 6 lactating women who were at least 12 weeks postpartum and had elected to wean their infants. The women were given 40 mg of Duloxetine Capsules twice daily for 3.5 days. The peak concentration measured in breast milk occurred at a median of 3 hours after the dose. The amount of Duloxetine Capsules in breast milk was approximately 7 mcg/day while on that dose; the estimated daily infant dose was approximately 2 mcg/kg/day, which is less than 1% of the maternal dose. The presence of Duloxetine Capsules metabolites in breast milk was not examined..

Paediatric Use

The safety and effectiveness of Duloxetine Capsules have been established for treatment of generalized anxiety disorder (GAD) in patients 7 to 17 years of age and for treatment of juvenile fibromyalgia syndrome in patients 13 to 17 years of age. The safety and effectiveness of Duloxetine Capsules have not been established in pediatric patients with major depressive disorder (MDD), diabetic peripheral neuropathic pain, or chronic musculoskeletal pain.

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric patients. Monitor all pediatric patients being treated with antidepressants for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment, or at times of dosage changes. Perform regular monitoring of weight and growth in pediatric patients treated with Duloxetine Capsules.

Generalized Anxiety Disorder

Use of Duloxetine Capsules for the treatment of GAD in patients 7 to 17 years of age is supported by one 10-week, placebo-controlled trial (GAD-6). The study included 272 pediatric patients with GAD of which 47% were 7 to 11 years of age (53% were 12 to 17 years of age). Duloxetine Capsules

demonstrated superiority over placebo as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score.

The safety and effectiveness of Duloxetine Capsules for the treatment of GAD in pediatric patients less than 7 years of age have not been established.

Fibromyalgia

Use of Duloxetine Capsules for treatment of fibromyalgia in patients 13 to 17 years of age is supported by a 13-week placebo-controlled trial in 184 patients with juvenile fibromyalgia syndrome (Study FM-4). Duloxetine Capsules showed improvement over placebo on the primary endpoint, change from baseline to end-of-treatment on the Brief Pain Inventory (BPI) – Modified Short Form: Adolescent Version 24-hour average pain severity rating.

The safety and effectiveness of Duloxetine Capsules for the treatment of fibromyalgia in patients less than 13 years of age have not been established.

Major Depressive Disorder

The safety and effectiveness of Duloxetine Capsules have not been established in pediatric patients for the treatment of MDD. Efficacy of Duloxetine Capsules was not demonstrated in two 10-week, placebo-controlled trials with 800 pediatric patients aged 7 to 17 years old with MDD (MDD-6 and MDD-7). Neither Duloxetine Capsules nor an active control (approved for treatment of pediatric MDD) was superior to placebo.

The most frequently observed adverse reactions in the MDD pediatric clinical trials included nausea, headache, decreased weight, and abdominal pain. Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs.

Juvenile Animal Toxicology Data

Duloxetine administration to young rats from post-natal day 21 (weaning) through post-natal day 90 (adult) resulted in decreased body weights that persisted into adulthood, but recovered when drug treatment was discontinued; slightly delayed (~1.5 days) sexual maturation in females, without any effect on fertility; and a delay in learning a complex task in adulthood, which was not observed after drug treatment was discontinued. These effects were observed at the high dose of 45 mg/kg/day (2 times the MRHD, for a child); the no-effect-level was 20 mg/kg/day (≈1 times the MRHD, for a child).

Geriatric Use

Geriatric Exposure in Premarketing Clinical Trials of Duloxetine Capsules.

Of the 2,418 patients in MDD trials, 6% (143) were 65 years of age or over.

Of the 1041 patients in CLBP trials, 21% (221) were 65 years of age or over.

Of the 487 patients in OA trials, 41% (197) were 65 years of age or over.

Of the 1,074 patients in the DPNP trials, 33% (357) were 65 years of age or over.

Of the 1,761 patients in FM trials, 8% (140) were 65 years of age or over.

In the MDD, GAD, DPNP, FM, OA, and CLBP studies, no overall differences in safety or effectiveness were generally observed between these patients and younger adult patients, and other reported clinical experience has not identified differences in responses between these geriatric and younger adult patients, but greater sensitivity of some older patients cannot be ruled out.

SSRIs and SNRIs, including Duloxetine Capsules have been associated with clinically significant hyponatremia in geriatric patients, who may be at greater risk for this adverse reaction.

In an analysis of data from all placebo-controlled-trials, Duloxetine Capsules -treated patients reported a higher rate of falls compared to placebo-treated patients. The increased risk appears to be proportional to a patient's underlying risk for falls. Underlying risk appears to increase steadily with age. As geriatric patients tend to have a higher prevalence of risk factors for falls such as medications, medical comorbidities and gait disturbances, the impact of increasing age by itself on falls during Duloxetine Capsules treatment is unclear. Falls with serious consequences including bone fractures and hospitalizations have been reported with Duloxetine Capsules use.

The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no difference in the Cmax, but the AUC of duloxetine was somewhat (about 25%) higher and the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for clearance decrease by approximately 1% for each year of age between 25 to 75 years of age; but age as a predictive factor only accounts for a small percentage of between-patient variability. Dosage adjustment based on the age of the adult patient is not necessary.

Gender

Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status

Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race

No specific pharmacokinetic study was conducted to investigate the effects of race.

Hepatic Impairment

Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination. After a single 20 mg dose of Duloxetine Capsules, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although Cmax was similar to normals in the cirrhotic patients, the half-life was about 3 times longer.

Severe Renal Impairment

Limited data are available on the effects of Duloxetine Capsules in patients with end-stage renal disease (ESRD). After a single 30 mg dose of Duloxetine Capsules, Cmax and AUC values were approximately 100% greater in patients with ESRD receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6- methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. Population PK analyses suggest that mild to moderate degrees of renal impairment (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance.

Drug Abuse and Dependence

Abuse

In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential.

While Duloxetine Capsules has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Duloxetine Capsules (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence

In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

The following serious adverse reactions are described below and elsewhere in the labeling:

- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

- Hepatotoxicity
- Orthostatic Hypotension, Falls and Syncope
- Serotonin Syndrome
- Increased Risk of Bleeding
- Severe Skin Reactions
- Discontinuation Syndrome
- Activation of Mania/Hypomania
- Angle-Closure Glaucoma
- Seizures Increases in Blood Pressure
- Clinically Important Drug Interactions
- Hyponatremia
- Urinary Hesitation and Retention

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The stated frequencies of adverse reactions represent the proportion of patients who experienced, at least once, one treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Reactions in Adults

Adult Clinical Trial Database

The data described below reflect exposure to Duloxetine Capsules in placebo-controlled adult trials for MDD (N=3779), GAD (N=1018), OA (N=503), CLBP (N=300), DPNP (N=906), and FM (N=1294). The age range in this pooled population was 17 to 89 years of age. In this pooled population, 66%, 61%, 61%, 43%, and 94% of adult patients were female; and 82%, 73%, 85%, 74%, and 86% of adult patients were Caucasian in the MDD, GAD, OA and CLBP, DPNP, and FM populations, respectively. Most patients received Duloxetine Capsules dosages of a total of 30 to 120 mg per day.The data below do not include results of the trial that evaluated the efficacy of Duloxetine Capsules for the treatment of

GAD in patients ≥65 years old (Study GAD-5), however, the adverse reactions observed in this geriatric population were generally similar to adverse reactions in the overall adult population.

Adverse Reactions Leading to Treatment Discontinuation in Adult Placebo-Controlled Trials

Major Depressive Disorder

Approximately 8.4% (319/3779) of Duloxetine Capsules -treated patients in placebo-controlled adult trials for MDD discontinued treatment due to an adverse reaction, compared with 4.6% (117/2536) of placebo-treated patients. Nausea (Duloxetine Capsules 1.1%, placebo 0.4%) was the only adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the Duloxetine Capsules-treated patients and at a rate of at least twice that of placebo-treated patients).

Generalized Anxiety Disorder

Approximately 13.7% (139/1018) of the Duloxetine Capsules -treated patients in placebo-controlled adult trials for GAD discontinued treatment due to an adverse reaction, compared with 5% (38/767) for placebo-treated patients. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (Duloxetine Capsules 3.3%, placebo 0.4%), and dizziness (Duloxetine Capsules 1.3%, placebo 0.4%).

Diabetic Peripheral Neuropathic Pain

Approximately 12.9% (117/906) of the Duloxetine Capsules -treated patients in placebo-controlled adult trials for DPNP discontinued treatment due to an adverse reaction, compared with 5.1% (23/448) for placebo-treated patients. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (Duloxetine Capsules 3.5%, placebo 0.7%), dizziness (Duloxetine Capsules 1.2%, placebo 0.4%), and somnolence (Duloxetine Capsules 1.1%, placebo 0%).

Fibromyalgia

Approximately 17.5% (227/1294) of the Duloxetine Capsules -treated patients in 3- to 6-month placebo-controlled adult trials for FM discontinued treatment due to an adverse reaction, compared with 10.1% (96/955) for placebo-treated patients. Adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (Duloxetine Capsules 2.0%, placebo 0.5%), headache (Duloxetine Capsules 1.2%, placebo 0.3%), somnolence (Duloxetine Capsules 1.1%, placebo 0%), and fatigue (Duloxetine Capsules 1.1%, placebo 0.1%).

Chronic Pain due to Osteoarthritis

Approximately 15.7% (79/503) of the Duloxetine Capsules -treated patients in 13-week, placebo-controlled adult trials for chronic pain due to OA discontinued treatment due to an adverse reaction, compared with 7.3% (37/508) for placebo-treated patients. Adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (Duloxetine Capsules 2.2%, placebo 1%).

Chronic Low Back Pain

Approximately 16.5% (99/300) of the Duloxetine Capsules -treated patients in 13-week, placebo-controlled adult trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% (28/441) for placebo-treated patients. Adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (Duloxetine Capsules 3%, placebo 0.7%), and somnolence (Duloxetine Capsules 1%, placebo 0%).

Most Common Adverse Reactions in Adult Trials

The most commonly observed adverse reactions in Duloxetine Capsules -treated patients (as defined above) were:

Diabetic Peripheral Neuropathic Pain: nausea, somnolence, decreased appetite, constipation, hyperhidrosis, and dry mouth.

Fibromyalgia: nausea, dry mouth, constipation, somnolence, decreased appetite, hyperhidrosis, and agitation.

Chronic Pain due to Osteoarthritis: nausea, fatigue, constipation, dry mouth, insomnia, somnolence, and dizziness.

Chronic Low Back Pain: nausea, dry mouth, insomnia, somnolence, constipation, dizziness, and fatigue.

The most commonly observed adverse reactions in Duloxetine Capsules -treated patients in all the pooled adult populations (i.e., MDD, GAD, DPNP, FM, OA, and CLBP) (incidence of at least 5% and at least twice the incidence in placebo-treated patients) were nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

TABLE 2 displays the incidence of adverse reactions in placebo-controlled trials for approved adult populations (i.e., MDD, GAD, DPNP, FM, OA, and CLBP) that occurred in 5% or more of Duloxetine Capsules -treated patients and with an incidence greater than placebo-treated patients.

Table 2: Adverse Reactions: Incidence of 5% or More and Greater than Placebo in Placebo-Controlled Trials of Approved Adult Populations[a]

Adverse Reaction	Percentage of Patients Reporting Reaction	
	Duloxetine Capsules (N=8100)	Placebo (N=5655)
Nausea[c]	23	8
Headache	14	12
Dry mouth	13	5
Somnolence[e]	10	3
Fatigue[b,c]	9	5
Insomnia[d]	9	5
Constipation[c]	9	4
Dizziness[c]	9	5
Diarrhea	9	6
Decreased appetite[c]	7	2
Hyperhidrosis[c]	6	1
Abdominal pain[f]	5	4

a Includes adults with MDD, GAD, DPNP, FM, and chronic musculoskeletal pain. The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.

b Also includes asthenia.

c Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

d Also includes initial insomnia, middle insomnia, and early morning awakening.

e Also includes hypersomnia and sedation.

f Also includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.

Adverse Reactions in Pooled MDD and GAD Trials in Adults

TABLE 3 displays the incidence of adverse reactions in MDD and GAD placebo-controlled adult trials that occurred in 2% or more of Duloxetine Capsules -treated patients and with an incidence greater than placebo-treated patients.

Table 3: Adverse Reactions: Incidence of 2% or More and Greater than Placebo in MDD and GAD Placebo-Controlled Trials in Adults[a,b]

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Duloxetine Capsules (N=3303)	**Placebo (N=2352)**
Gastrointestinal Disorders		
Nausea	23	7
Dry Mouth[b]	11	3
Constipation[b]	10	3
Diarrhea	9	5
Abdominal Pain[c]	5	4
Vomiting	3	2
Dyspepsia	2	1
General Disorders and Administration Site Conditions		
Fatigue[d]	11	5
Infections and Infestations		
Nasopharyngitis	4	4
Upper Respiratory Tract Infection	3	3
Influenza	2	2
Metabolism and Nutrition Disorders		
Decreased Appetite[b]	8	1
Musculoskeletal and Connective Tissue		
Musculoskeletal Pain[e]	3	3
Muscle Spasms	2	2
Nervous System Disorders		
Headache	13	8
Somnolence[b,f]	11	3
Dizziness	9	5
Paraesthesia[g]	2	2
Tremor[b]	2	<1
Psychiatric Disorders		
Insomnia[b,h]	10	5

Agitation[i]	3	1
Reproductive System and Breast Disorders		
Erectile Dysfunction[b]	4	<1
Ejaculation Disorder[j]	2	<1
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	2	2
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	6	1
Vascular Disorders		
Flushing[k]	3	1
Blood pressure increased[l]	2	1

a The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.

b Incidence of 120 mg/day is significantly greater than the incidence for 30 mg/day.

c Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, abdominal tenderness and gastrointestinal pain.

d Includes asthenia.

e Includes myalgia and neck pain.

f Includes hypersomnia and sedation.

g Includes hypoaesthesia, facial hypoaesthesia, genital hypoaesthesia and oral paraesthesia.

h Includes initial insomnia, middle insomnia, and early morning awakening.

i Includes feeling jittery, nervousness, restlessness, tension and psychomotor hyperactivity.

j Includes ejaculation failure.

k Includes hot flush.

l Includes increased diastolic blood pressure, increased systolic blood pressure, diastolic hypertension, essential hypertension, hypertension, hypertensive crisis, labile hypertension, orthostatic hypertension, secondary hypertension, and systolic hypertension.

Effects on Male and Female Sexual Function in Adults with MDD

Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment.

Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual adverse reactions, was used prospectively in 4 MDD placebo-controlled adult trials (Studies MDD-1, MDD-2, MDD-3, and MDD-4). The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction. Positive numbers signify a worsening of sexual function from baseline. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients.

In these trials, Duloxetine Capsules -treated male patients experienced significantly more sexual dysfunction, as measured by the total score on the ASEX and the ability to reach orgasm, than placebo-treated male patients (see TABLE 5). Duloxetine Capsules-treated female patients did not experience more sexual dysfunction than placebo-treated female patients as measured by ASEX total score. Healthcare providers should routinely inquire about possible sexual adverse reactions in Duloxetine Capsules -treated patients.

Table 5: Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Adult Trials

Male Patients[a]		**Female Patients[a]**		
	Duloxetine Capsules (n=175)	**Placebo (n=83)**	**Duloxetine Capsules (n=241)**	**Placebo**
ASEX Total (Items 1-5)	0.56[b]	-1.07	-1.15	(n=126)
Item 1 — Sex drive	-0.07	-0.12	-0.32	-1.07
Item 2 — Arousal	0.01	-0.26	-0.21	-0.24
Item 3 — Ability to achieve erection (men); Lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4 — Ease of reaching orgasm	0.40[c]	-0.24	-0.09	-0.18
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.13

a n=Number of patients with non-missing change score for ASEX total.

b p=0.013 versus placebo.

c p<0.001 versus placebo.

Vital Sign Changes in Adults

In placebo-controlled clinical trials across approved adult populations for change from baseline to endpoint, Duloxetine Capsules -treated patients had mean increases of 0.23 mm Hg in systolic blood pressure (SBP) and 0.73 mm Hg in diastolic blood pressure (DBP) compared to mean decreases of 1.09 mm Hg in SBP and 0.55 mm Hg in DBP in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure.

Duloxetine Capsules treatment, for up to 26 weeks in placebo-controlled trials across approved adult populations, typically caused a small increase in heart rate for change from baseline to endpoint compared to placebo of up to 1.37 beats per minute (increase of 1.20 beats per minute in Duloxetine Capsules -treated patients, decrease of 0.17 beats per minute in placebo-treated patients).

Laboratory Changes in Adults

Duloxetine Capsules treatment in placebo-controlled clinical trials across approved adult populations, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Duloxetine Capsules -treated patients when compared with placebo-treated patients. High bicarbonate, cholesterol, and abnormal (high or low) potassium, were observed more frequently in Duloxetine Capsules -treated patients compared to placebo-treated patients.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Duloxetine Capsules in Adults

Following is a list of adverse reactions reported by patients treated with Duloxetine Capsules in clinical adult trials. In clinical trials of all approved adult populations, 34,756 patients were treated with Duloxetine Capsules. Of these, 27% (9337) took Duloxetine Capsules for at least 6 months, and 12% (4317) took Duloxetine Capsules for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

Cardiac Disorders — Frequent: palpitations; Infrequent: myocardial infarction, tachycardia, and Takotsubo cardiomyopathy.

Ear and Labyrinth Disorders — Frequent: vertigo; Infrequent: ear pain and tinnitus.

Endocrine Disorders — Infrequent: hypothyroidism.

Eye Disorders — Frequent: vision blurred; Infrequent: diplopia, dry eye, and visual impairment.
Gastrointestinal Disorders — Frequent: flatulence; Infrequent: dysphagia, eructation, gastritis, gastrointestinal hemorrhage, halitosis, and stomatitis; Rare: gastric ulcer.
General Disorders and Administration Site Conditions — Frequent: chills/rigors; Infrequent: falls, feeling abnormal, feeling hot and/or cold, malaise, and thirst; Rare: gait disturbance.
Infections and Infestations — Infrequent: gastroenteritis and laryngitis.
Investigations — Frequent: weight increased, weight decreased; Infrequent: blood cholesterol increased.
Metabolism and Nutrition Disorders — Infrequent: dehydration and hyperlipidemia; Rare: dyslipidemia.
Musculoskeletal and Connective Tissue Disorders — Frequent: musculoskeletal pain; Infrequent: muscle tightness and muscle twitching.
Nervous System Disorders — Frequent: dysgeusia, lethargy, and paraesthesia/hypoesthesia; Infrequent: disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; Rare: dysarthria.
Psychiatric Disorders — Frequent: abnormal dreams and sleep disorder; Infrequent: apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; Rare: completed suicide.
Renal and Urinary Disorders — Frequent: urinary frequency; Infrequent: dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal.
Reproductive System and Breast Disorders — Frequent: anorgasmia/orgasm abnormal; Infrequent: menopausal symptoms, sexual dysfunction, and testicular pain; Rare: menstrual disorder.
Respiratory, Thoracic and Mediastinal Disorders — Frequent: yawning, oropharyngeal pain; Infrequent: throat tightness.
Skin and Subcutaneous Tissue Disorders — Frequent: pruritus; Infrequent: cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; Rare: ecchymosis.
Vascular Disorders — Frequent: hot flush; Infrequent: flushing, orthostatic hypotension, and peripheral coldness.

Adverse Reactions Observed in Placebo-Controlled Clinical Trials in Pediatric Patients

Pediatric Clinical Trial Database

The data described below reflect exposure to Duloxetine Capsules (N=567) in pediatric patients aged 7 to 18 years of age from two 10-week, placebo-controlled trials in patients with MDD (N=341) (Studies MDD-6 and MDD-7), one 10-week placebo-controlled trial in GAD (N=135) (Study GAD-6), and a 13-week trial in fibromyalgia (N=91). Duloxetine Capsules is not approved for the treatment of MDD in pediatric patients. Of the Duloxetine Capsules -treated patients in these studies, 36% were 7 to 11 years

of age (64% were between 12 to 18 years old), 55% were female, and 69% were Caucasian. Patients received 30 to 120 mg of Duloxetine Capsules per day during placebo-controlled acute treatment studies. In the pediatric MDD, GAD, and fibromyalgia trials up to 40 weeks long, there were 988 Duloxetine Capsules -treated pediatric patients aged 7 to 17 years of age (most patients received 30-120 mg per day) – 35% were 7 to 11 years of age (65% were 12 to 17 years old) and 56% were female.

Most Common Adverse Reactions in Pediatric Trials

The most common adverse reactions (≥5% in Duloxetine Capsules -treated patients and at least twice the incidence of placebo-treated patients) in all pooled pediatric populations (MDD, GAD, and fibromyalgia) were decreased weight, decreased appetite, nausea, vomiting, fatigue, and diarrhea.

Adverse Reactions in Pediatric Patients Aged 7 to 17 Years Old with MDD and GAD

The adverse reaction profile observed in clinical trials in pediatric patients aged 7 to 18 years old with MDD and GAD was consistent with the adverse reaction profile observed in adult clinical trials. The most common (≥5% and twice placebo) adverse reactions observed in these pediatric clinical trials included: nausea, diarrhea, decreased weight, and dizziness.

TABLE 6 provides the incidence of adverse reactions in MDD and GAD pediatric placebo-controlled trials that occurred in greater than 2% of patients treated with Duloxetine Capsules and with an incidence greater than patients treated with placebo. Duloxetine Capsules is not approved in the treatment of MDD in pediatric patients.

Table 6: Adverse Reactions: Incidence of 2% or More and Greater than Placebo in Three 10- week Pediatric Placebo-Controlled Trials in MDD and GAD[a]

System Organ Class/Adverse Reaction	Percentage of Pediatric Patients Reporting Reaction	
	Duloxetine Capsules (N=476)	Placebo (N=362)
Gastrointestinal Disorders		
Nausea	18	8
Abdominal Pain[b]	13	10
Vomiting	9	4
Diarrhea	6	3
Dry Mouth	2	1
General Disorders and Administration Site Conditions		
Fatigue[c]	7	5
Investigations		
Decreased Weight[d]	14	6
Metabolism and Nutrition Disorders		
Decreased Appetite	10	5

Nervous System Disorders		
Headache	18	13
Somnolence[e]	11	6
Dizziness	8	4
Psychiatric Disorders		
Insomnia[f]	7	4
Respiratory, Thoracic, and Mediastinal Disorders		
Oropharyngeal Pain	4	2
Cough	3	1

a Duloxetine Capsules is not approved for the treatment of pediatric MDD. The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.

b Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain.

c Also includes asthenia.

d Frequency based on weight measurement meeting potentially clinically significant threshold of ≥3.5% weight loss (N=467 Duloxetine Capsules; N=354 Placebo).

e Also includes hypersomnia and sedation.

f Also includes initial insomnia, insomnia, middle insomnia, and terminal insomnia.

Other adverse reactions that occurred at an incidence of less than 2% and were reported by more Duloxetine Capsules -treated patients than placebo-treated patients in pediatric MDD and GAD clinical trials included: abnormal dreams (including nightmare), anxiety, flushing (including hot flush), hyperhidrosis, palpitations, pulse increased, and tremor (Duloxetine Capsules is not approved to treat pediatric patients with MDD).

The most commonly reported symptoms following discontinuation of Duloxetine Capsules in pediatric MDD and GAD clinical trials included headache, dizziness, insomnia, and abdominal pain.

Growth (Height and Weight) in Pediatric Patients 7 to 17 Years Old with GAD and MDD

Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Duloxetine Capsules -treated pediatric patients in clinical trials experienced a 0.1 kg mean decrease in weight at 10 weeks, compared with a mean weight gain of approximately 0.9 kg in placebo-treated pediatric patients. The proportion of patients who experienced a clinically significant decrease in weight (≥3.5%) was greater in the Duloxetine Capsules group than in the placebo group (16% and 6%, respectively). Subsequently, over the 4- to 6-month uncontrolled extension periods, Duloxetine

Capsules -treated patients on average trended toward recovery to their expected baseline weight percentile based on population data from age- and sex-matched peers.

In studies up to 9 months, Duloxetine Capsules -treated pediatric patients experienced an increase in height of 1.7 cm on average (2.2 cm increase in patients 7 to 11 years of age and 1.3 cm increase in patients 12 to 17 years of age). While height increase was observed during these studies, a mean decrease of 1% in height percentile was observed (decrease of 2% in patients 7 to 11 years of age and increase of 0.3% in patients 12 to 17 years of age). Weight and height should be monitored regularly in pediatric patients treated with Duloxetine Capsules.

Adverse Reactions in Pediatric Patients Aged 13 to 17 Years Old with Fibromyalgia

TABLE 7 provides the incidence of adverse reactions in a fibromyalgia pediatric placebo-controlled trial (Study FM-4) that occurred in greater than 5% of patients treated with Duloxetine Capsules and with an incidence greater than patients treated with placebo.

Table 7: Adverse Reactions: Incidence of 5% or More and Greater than Placebo in a 13-week Placebo-Controlled Trial in Pediatric Patients 13 to 17 Years Old with Fibromyalgia (Study FM-4)[a]

	Duloxetine Capsules (N=91)	**Placebo (N=93)**
Nausea	25%	15%
Decreased appetite	15%	3%
Vomiting	15%	5%
Decreased weight[b]	15%	5%
Headache	14%	11%
Nasopharyngitis	9%	2%
Somnolence	9%	3%
Upper respiratory tract infection	7%	2%
Viral gastroenteritis	5%	0%
Fatigue	5%	2%

a The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.

b Frequency based on weight measurement meeting potentially clinically significant threshold of ≥3.5% weight loss (N=89 Duloxetine Capsules; N=92 Placebo).

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Duloxetine Capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally related to Duloxetine Capsules therapy and not mentioned elsewhere in labeling include: acute pancreatitis, anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, angle-closure glaucoma, colitis (microscopic or unspecified), cutaneous vasculitis (sometimes associated with systemic involvement), extrapyramidal disorder, galactorrhea, gynecological bleeding, hallucinations, hyperglycemia, hyperprolactinemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, restless legs syndrome, seizures upon treatment discontinuation, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

4.9 Overdose

Signs and Symptoms

In postmarketing experience, fatal outcomes have been reported for acute Duloxetine Capsules overdoses, primarily with mixed overdoses, but also with Duloxetine Capsules only, including 1000 mg of Duloxetine Capsules (approximately 8.3 times the maximum recommended dosage). Signs and symptoms of overdose (Duloxetine Capsules alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

Management of Overdose

There is no specific antidote to a Duloxetine Capsules overdosage, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered.

In case of acute overdose with Duloxetine Capsules, treatment should consist of those general measures employed in the management of overdose with any drug, such as assuring an adequate airway, oxygenation, and ventilation and monitoring cardiac rhythm and vital signs. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Induction of emesis is not recommended.

Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease duloxetine AUC and Cmax by an average of one-third, although some patients had a limited effect of activated charcoal. Due to the large volume of distribution of duloxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.

In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who overdose with Duloxetine Capsules and tricyclic antidepressants. In such a case, decreased clearance of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Depressants, ATC code: N06AX21

Mechanism of action

Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.

Pharmacodynamics

Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors in vitro. Duloxetine does not inhibit monoamine oxidase (MAO).

Duloxetine Capsules is in a class of drugs known to affect urethral resistance.

Cardiac Electrophysiology

The effect of Duloxetine Capsules 130 mg and 200 mg administered twice daily (2.7 and 3.3 times the maximum recommended dosage, respectively) to steady state was evaluated in a randomized, double-blinded, two-way crossover study in 117 healthy female adult subjects. No QT interval prolongation was detected. Duloxetine Capsules appears to be associated with concentration-dependent but not clinically meaningful QT shortening.

5.2 Pharmacokinetic properties

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP1A2 and CYP2D6.

Absorption

After oral Duloxetine Capsules administration, duloxetine hydrochloride is well absorbed. There is a median 2 hour lag until absorption begins (Tlag), with maximal plasma concentrations (Cmax) of

duloxetine occurring 6 hours post dose. There is a 3 hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

Effect of Food: Food does not affect the Cmax of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%.

Distribution

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α1-acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Elimination

Metabolism

Biotransformation and disposition of duloxetine in humans have been determined following oral administration of 14C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 catalyze the oxidation of the naphthyl ring in vitro. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate.

Excretion

Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the faeces. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

Specific Populations

Pediatric Patients

Duloxetine steady-state plasma concentration was comparable in pediatric patients 7 to 17 years of age and adult patients. The average steady-state duloxetine concentration was approximately 30% lower in this pediatric population relative to adult patients. The model-predicted duloxetine steady state plasma

concentrations in pediatric patients 7 to 17 years of age were mostly within the concentration range observed in adult patients and did not exceed the concentration range in adults.

5.3 Preclinical safety data

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (3 times the maximum recommended human dose (MRHD) of 120 mg/day given to children on a mg/m2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (1 time the MRHD given to children). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (2 times the MRHD given to children).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (1 time the MRHD given to children) and up to 36 mg/kg/day in males (1.4 times the MRHD given to children) did not increase the incidence of tumors.

Mutagenesis

Duloxetine was not mutagenic in the in vitro bacterial reverse mutation assay (Ames test) and was not clastogenic in an in vivo chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an in vitro mammalian forward gene mutation assay in mouse lymphoma cells or in an in vitro unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow in vivo.

Impairment of Fertility

Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (3 times the MRHD given to adolescents on a mg/m2 basis) did not alter mating or fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres, (Pharmaspheres 710-850µ) (#20/25), Hypromellose 2910, 5cps, (Methocel E5 LV Premium), Crospovidone, (Kollidon CL M), Talc, (Luzenac Pharma), Sucrose, P.G Sugar # 40 # 80, HPMC AS 716 F, (ENTERACT), Triethyl citrate, Iso Propyl alcohol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Blister pack

3 x 10's Alu-PVC Blister pack.

6.6 Instructions for use and handling and disposal

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

7. Manufacturing Authorization Holder & Manufactured by:

Manufactured by:

HETERO LABS LIMITED

M/s. Hetero Labs Limited (Unit-I),

Village: Kalyanpur, Chakkan Road,

Tehsil: Baddi, Distt. Solan,

Himachal Pradesh – 173205, India.

MARKETING AUTHORISATION HOLDER

Hetero Labs Limited ,

7-2-A2, Hetero corporate, Industrial Estates,

Sanath nagar, Hyderabad -500018,

Telangana, INDIA.

8. Marketing Authorization Number

CTD11352

9. Date of first Authorization /renewal of the authorization

10/12/2025

10. Date of revision

10/12/2025