[g] Also includes initial insomnia, middle insomnia, and early morning awakening
[h] Also includes feeling jittery, nervousness, restlessness, tension and psychomotor hyperactivity
[i] Also includes loss of libido
[j] Also includes anorgasmia

DPNP, FM, OA, and CLBP — Table 4 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with CYMBALTA (determined prior to rounding) in the premarketing acute phase of DPNP, FM, OA, and CLBP placebo-controlled trials and with an incidence greater than placebo.

Table 4: Treatment-Emergent Adverse Reactions: Incidence of 2% or More and Greater than Placebo in DPNP, FM, OA, and CLBP Placebo-Controlled Trials[a]

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	CYMBALTA (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 60 mg/day.
[c] Also includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness and gastrointestinal pain
[d] Also includes asthenia

[e] Also includes myalgia and neck pain
[f] Also includes hypersomnia and sedation
[g] Also includes hypoaesthesia, hypoaesthesia facial, genital hypoaesthesia and paraesthesia oral
[h] Also includes initial insomnia, middle insomnia, and early morning awakening.
[i] Also includes feeling jittery, nervousness, restlessness, tension and psychomotor hyperactivity
[j] Also includes ejaculation failure
[k] Also includes hot flush
[l] Also includes blood pressure diastolic increased, blood pressure systolic increased, diastolic hypertension, essential hypertension, hypertension, hypertensive crisis, labile hypertension, orthostatic hypertension, secondary hypertension, and systolic hypertension

6.6 Effects on Male and Female Sexual Function in Adults

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 side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in Table 5 below, patients treated with CYMBALTA experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with CYMBALTA experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on CYMBALTA than on placebo as measured by ASEX total score. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

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

	Male Patients[a]		Female Patients[a]	
	CYMBALTA (n=175)	**Placebo (n=83)**	**CYMBALTA (n=241)**	**Placebo (n=126)**
ASEX Total (Items 1-5)	0.56[b]	-1.07	-1.15	-1.07
Item 1 — Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2 — Arousal	0.01	-0.26	-0.21	-0.18
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	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

[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

6.7 Vital Sign Changes in Adults

In placebo-controlled clinical trials across approved indications for change from baseline to endpoint, CYMBALTA treatment was associated with mean increases of 0.23 mm Hg in systolic blood pressure and 0.73 mm Hg in diastolic blood pressure compared to mean decreases of 1.09 mm Hg systolic and 0.55 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure *[see Warnings and Precautions (5.3, 5.11)]*.

CYMBALTA treatment, for up to 26 weeks in placebo-controlled trials across approved indications, 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 CYMBALTA-treated patients, decrease of 0.17 beats per minute in placebo-treated patients).

6.8 Laboratory Changes in Adults

CYMBALTA treatment in placebo-controlled clinical trials across approved indications, 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 CYMBALTA-treated patients when compared with placebo-treated patients *[see Warnings and Precautions (5.2)]*. High bicarbonate, cholesterol, and abnormal (high or low) potassium, were observed more frequently in CYMBALTA treated patients compared to placebo.

6.9 Electrocardiogram Changes in Adults

The effect of CYMBALTA 160 mg and 200 mg administered twice daily to steady state was evaluated in a randomized, double-blinded, two-way crossover study in 117 healthy female subjects. No QT interval prolongation was

detected. CYMBALTA appears to be associated with concentration-dependent but not clinically meaningful QT shortening.

6.10 Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of CYMBALTA in Adults

Following is a list of treatment-emergent adverse reactions reported by patients treated with CYMBALTA in clinical trials. In clinical trials of all indications, 34,756 patients were treated with CYMBALTA. Of these, 26.9% (9337) took CYMBALTA for at least 6 months, and 12.4% (4317) 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.

6.11 Adverse Reactions Observed in Children and Adolescent Placebo-Controlled Clinical Trials

The adverse drug reaction profile observed in pediatric clinical trials (children and adolescents) was consistent with the adverse drug reaction profile observed in adult clinical trials. The specific adverse drug reactions observed in adult patients can be expected to be observed in pediatric patients (children and adolescents) *[see Adverse Reactions (6.5)]*. The most common (≥5% and twice placebo) adverse reactions observed in pediatric clinical trials include: nausea, diarrhea, decreased weight, and dizziness.

Table 6 provides the incidence of treatment-emergent adverse reactions in MDD and GAD pediatric placebo-controlled trials that occurred in greater than 2% of patients treated with CYMBALTA and with an incidence greater than placebo.

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

System Organ Class/Adverse Reaction	Percentage of Pediatric Patients Reporting Reaction	
	CYMBALTA (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] 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 CYMBALTA; 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% but were reported by more CYMBALTA treated patients than placebo treated patients and are associated CYMBALTA treatment: abnormal dreams (including nightmare), anxiety, flushing (including hot flush), hyperhidrosis, palpitations, pulse increased, and tremor.

Discontinuation-emergent symptoms have been reported when stopping CYMBALTA. The most commonly reported symptoms following discontinuation of CYMBALTA in pediatric clinical trials have included headache, dizziness, insomnia, and abdominal pain *[see Warnings and Precautions (5.7) and Adverse Reactions (6.2)]*.

Growth (Height and Weight) — Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Pediatric patients treated with CYMBALTA in clinical trials experienced a 0.1kg mean decrease in weight at 10 weeks, compared with a mean weight gain of approximately 0.9 kg in placebo-treated patients. The proportion of patients who experienced a clinically significant decrease in weight (≥3.5%) was greater in the CYMBALTA group than in the placebo group (14% and 6%, respectively). Subsequently, over the 4- to 6-month uncontrolled extension periods, CYMBALTA-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, CYMBALTA-treated pediatric patients experienced an increase in height of 1.7 cm on average (2.2 cm increase in children [7 to 11 years of age] and 1.3 cm increase in adolescents [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 children [7 to 11 years of age] and increase of 0.3% in adolescents [12 to 17 years of age]). Weight and height should be monitored regularly in children and adolescents treated with CYMBALTA.

6.12 Postmarketing Spontaneous Reports

The following adverse reactions have been identified during post approval use of CYMBALTA. 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 CYMBALTA 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.

7 DRUG INTERACTIONS

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

7.1 Inhibitors of CYP1A2

When duloxetine 60 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 C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin *[see Warnings and Precautions (5.12)]*.

7.2 Inhibitors of CYP2D6

Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, 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) *[see Warnings and Precautions (5.12)]*.

7.3 Dual Inhibition of CYP1A2 and CYP2D6

Concomitant administration of duloxetine 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 C_{max}.

7.4 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 60 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 is initiated or discontinued *[see Warnings and Precautions (5.5)]*.

7.5 Lorazepam

Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

7.6 Temazepam

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

7.7 Drugs that Affect Gastric Acidity

CYMBALTA 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, CYMBALTA, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using CYMBALTA 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 CYMBALTA with aluminum- and magnesium-containing antacids (51 mEq) or CYMBALTA 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 *[see Warnings and Precautions (5.14)]*.

7.8 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 (60 mg twice daily).

7.9 Drugs Metabolized by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold *[see Warnings and Precautions (5.12)]*.

7.10 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 *[see Drug Interactions (7.4)]*.

7.11 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.

7.12 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.

7.13 Monoamine Oxidase Inhibitors (MAOIs)

[See Dosage and Administration (2.8, 2.9), Contraindications (4), and Warnings and Precautions (5.4)].

7.14 Serotonergic Drugs

[See Dosage and Administration (2.8, 2.9), Contraindications (4), and Warnings and Precautions (5.4)].

7.15 Alcohol

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

In the CYMBALTA clinical trials database, three CYMBALTA-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 *[see Warnings and Precautions (5.2, 5.12)]*.

7.16 CNS Drugs

[See Warnings and Precautions (5.12)].

7.17 Drugs Highly Bound to Plasma Protein

Because duloxetine is highly bound to plasma protein, administration of CYMBALTA 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 (60 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) *[see Drug Interactions (7.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Pregnancy Exposure Registry — There is a pregnancy registry that monitors the pregnancy outcomes in women exposed to CYMBALTA during pregnancy. To enroll, contact the CYMBALTA Pregnancy Registry at 1-866-814-6975 or www.cymbaltapregnancyregistry.com.

Risk Summary — There are no adequate and well-controlled studies of CYMBALTA administration in pregnant women. In animal studies with duloxetine, fetal weights were decreased but there was no evidence of teratogenicity in pregnant rats and rabbits at oral doses administered during the period of organogenesis up to 4 and 7 times the maximum recommended human dose (MRHD) of 120 mg/day, respectively. 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. 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. CYMBALTA should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reaction — Neonates exposed during pregnancy to serotonin - norepinephrine reuptake inhibitors (SNRIs) or selective serotonin reuptake inhibitors (SSRIs) have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding which 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 features 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 *[see Warnings and Precautions (5.4)]*.

Data

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 teratogenicity at doses up to 45 mg/kg/day (4 times the maximum recommended human dose (MRHD) of 120 mg/day on a mg/m^2 basis, in rat; 7 times the MRHD in rabbit). 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; 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); 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.

8.3 Nursing Mothers

Risk Summary

CYMBALTA is present in human milk. In a published study, lactating women who were weaning their infants were given CYMBALTA. At steady state, the concentration of CYMBALTA in breast milk was approximately 25% that of maternal plasma. The estimated daily infant dose was approximately 0.14% of the maternal dose. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for CYMBALTA and any potential adverse effects on the milk-fed child from the drug or from the underlying maternal condition. Exercise caution when CYMBALTA is administered to a nursing woman.

Data

The disposition of CYMBALTA 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 CYMBALTA 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 CYMBALTA in breast milk was approximately 7 mcg/day while on that dose; the estimated daily infant dose was approximately 2 mcg/kg/day. The presence of CYMBALTA metabolites in breast milk was not examined.

8.4 Pediatric Use

Generalized Anxiety Disorder — In pediatric patients aged 7 to 17 years, efficacy was demonstrated in one 10-week, placebo-controlled trial. The study included 272 pediatric patients with GAD of which 47% were 7 to 11 years of age. CYMBALTA demonstrated superiority over placebo as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score *[see Clinical Studies (14.2)]*. The safety and effectiveness in pediatric patients less than 7 years of age have not been established.

Major Depressive Disorder — Efficacy was not demonstrated in two 10-week, placebo-controlled trials with 800 pediatric patients with MDD, age 7 to 17. Neither CYMBALTA nor an active control (indicated for treatment of pediatric depression) was superior to placebo. The safety and effectiveness in pediatric patients less than 7 years of age have not been established.

The most frequently observed adverse reactions in the 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. Perform regular monitoring of weight and growth in children and adolescents treated with an SNRI such as CYMBALTA *[see Adverse Reactions (6.11)]*.

Use of CYMBALTA in a child or adolescent must balance the potential risks with the clinical need *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Animal 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).

8.5 Geriatric Use

Of the 2,418 patients in premarketing clinical studies of CYMBALTA for MDD, 5.9% (143) were 65 years of age or over. Of the 1041 patients in CLBP premarketing studies, 21.2% (221) were 65 years of age or over. Of the 487 patients in OA premarketing studies, 40.5% (197) were 65 years of age or over. Of the 1,074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Of the 1,761 patients in FM premarketing studies, 7.9% (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 subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including CYMBALTA have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.13)]*.

In an analysis of data from all placebo-controlled-trials, patients treated with CYMBALTA reported a higher rate of falls compared to patients treated with placebo. The increased risk appears to be proportional to a patient's underlying risk for falls. Underlying risk appears to increase steadily with age. As elderly 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 treatment with CYMBALTA is unclear. Falls with serious consequences including bone fractures and hospitalizations have been reported *[see Warnings and Precautions (5.3) and Adverse Reactions (6.10)]*.

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 C_{max}, 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 patient is not necessary.

8.6 Gender

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

8.7 Smoking Status

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

8.8 Race

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

8.9 Hepatic Impairment

Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination. After a single 20 mg dose of CYMBALTA, 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 C_{max} was similar to normals in the cirrhotic patients, the half-life was about 3 times longer *[see Dosage and Administration (2.6) and Warnings and Precautions (5.14)]*.

8.10 Severe Renal Impairment

Limited data are available on the effects of duloxetine in patients with end-stage renal disease (ESRD). After a single 60 mg dose of duloxetine, C_{max} and AUC values were approximately 100% greater in patients with end-stage renal disease 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 *[see Dosage and Administration (2.6) and Warnings and Precautions (5.14)]*.

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

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

While CYMBALTA 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 CYMBALTA (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

9.3 Dependence

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

10 OVERDOSAGE

10.1 Signs and Symptoms

In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

10.2 Management of Overdose

There is no specific antidote to CYMBALTA, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

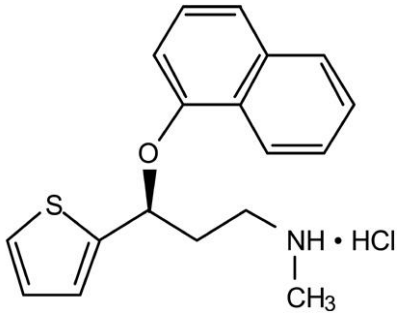
An adequate airway, oxygenation, and ventilation should be assured, and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease AUC and C_{max} by an average of one-third, although some subjects had a limited effect of activated charcoal. Due to the large volume of distribution of this drug, 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 are taking or have recently taken CYMBALTA and might ingest excessive quantities of a TCA. 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 *[see Warnings and Precautions (5.4) and Drug Interactions (7)]*. The physician should consider contacting a poison control center (1-800-222-1222 or www.poison.org) for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

11 DESCRIPTION

CYMBALTA® (duloxetine delayed-release capsules) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS$•HCl, which corresponds to a molecular weight of 333.88. The structural formula is:



Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 and 60 mg capsules also contain iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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).

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

12.3 Pharmacokinetics

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 and Distribution — Orally administered duloxetine hydrochloride is well absorbed. There is a median 2 hour lag until absorption begins (T_{lag}), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} 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%. 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.

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α_1-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.

Metabolism and Elimination — Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C-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. 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 feces. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

Children and Adolescents (ages 7 to 17 years) — Duloxetine steady-state plasma concentration was comparable in children (7 to 12 years of age), adolescents (13 to 17 years of age) and adults. The average steady-state duloxetine concentration was approximately 30% lower in the pediatric population (children and adolescents) relative to the adults.

The model-predicted duloxetine steady state plasma concentrations in children and adolescents were mostly within the concentration range observed in adult patients and did not exceed the concentration range in adults.

13 NONCLINICAL TOXICOLOGY

13.1 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 (6 times the maximum recommended human dose (MRHD) of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (2 times the MRHD). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (4 times the MRHD).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (2 times the MRHD) and up to 36 mg/kg/day in males (3 times the MRHD) 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 (4 times the MRHD) did not alter mating or fertility.

14 CLINICAL STUDIES

The efficacy of CYMBALTA has been established in the following adequate and well-controlled trials:

- Major Depressive Disorder (MDD): 4 short-term and 1 maintenance trial in adults *[see Clinical Studies (14.1)]*.
- Generalized Anxiety Disorder (GAD): 3 short-term trials in adults, 1 maintenance trial in adults, and 1 short-term trial in children and adolescents *[see Clinical Studies (14.2)]*.
- Diabetic Peripheral Neuropathic Pain (DPNP): Two 12-week trials in adults *[see Clinical Studies (14.3)]*.
- Fibromyalgia (FM): Two trials in adults (one of 3 months duration and one of 6 months duration) *[see Clinical Studies (14.4)]*.
- Chronic Musculoskeletal Pain: Two 12- to 13-week trials in adult patients with chronic low back pain (CLBP) and one 13-week trial in adult patients with chronic pain due to osteoarthritis *[see Clinical Studies (14.5)]*.

14.1 Major Depressive Disorder

The efficacy of CYMBALTA as a treatment for depression was established in 4 randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting DSM-IV criteria for major depression. In 2 studies, patients were randomized to CYMBALTA 60 mg once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for 9 weeks; in the third study, patients were randomized to CYMBALTA 20 or 40 mg twice daily (N=86 and N=91, respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were randomized to CYMBALTA 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks. There is no evidence that doses greater than 60 mg/day confer additional benefits.

In all 4 studies, CYMBALTA demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score (Studies 1-4 in Table 7).

In all of these clinical studies, analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

Table 7: Summary of the Primary Efficacy Results for Studies in Major Depressive Disorder

Study Number	Treatment Group	Primary Efficacy Measure: HAMD-17		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	CYMBALTA (60 mg/day)[b]	21.5 (4.10)	-10.9 (0.70)	-4.9 (-6.8, -2.9)
	Placebo	21.1 (3.71)	-6.1 (0.69)	--
Study 2	CYMBALTA (60 mg/day)[b]	20.3 (3.32)	-10.5 (0.71)	-2.2 (-4.0, -0.3)
	Placebo	20.5 (3.42)	-8.3 (0.67)	--
Study 3	CYMBALTA (20 mg BID)[b]	18.6 (5.85)	-7.4 (0.80)	-2.4 (-4.7, -0.2)
	CYMBALTA (40 mg BID)[b]	18.1 (4.52)	-8.6 (0.81)	-3.6 (-5.9, -1.4)
	Placebo	17.2 (5.11)	-5.0 (0.81)	--
Study 4	CYMBALTA (40 mg BID)[b]	19.9 (3.54)	-11.0 (0.49)	-2.2 (-3.6, -0.9)
	CYMBALTA (60 mg BID)[b]	20.2 (3.41)	-12.1 (0.49)	-3.3 (-4.7, -1.9)
	Placebo	19.9 (3.58)	-8.8 (0.50)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiplicity in trials where multiple dose groups were included.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.