

# Mixed Findings on Male Circumcision and HIV

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BOSTON — Male circumcision does not reduce the risk of HIV transmission from HIV-positive men to their female partners, but it does offer some protection to HIV-negative men and their female partners against the acquisition of genital infections associated with the spread of HIV, according to data presented at the 15th Conference on Retro-

viruses and Opportunistic Infections.

Heralded as “an HIV intervention that can really work,” male circumcision has previously been shown to reduce heterosexual acquisition of HIV in men, said Dr. Maria Wawer, a family health researcher at Johns Hopkins University, Baltimore, and cofounder of the Rakai (Uganda) Health Sciences Program—one of the largest HIV research, prevention, and care programs in Africa.

To determine whether the earlier find-

ings would also hold true with respect to rates of heterosexual transmission of the virus by HIV-positive men to their wives, Dr. Wawer and colleagues randomized more than 1,000 HIV-positive men to immediate or delayed (by 24 months) circumcision and asked the 770 men in the study who were married to invite their wives to participate. A total of 566 wives enrolled, of whom 245 were HIV negative. The investigators’ intent-to-treat analysis was based on 165 HIV-discordant couples,

including 94 in the male circumcision arm and 71 in the control arm.

The men in the study were examined postoperatively if they underwent circumcision and then at 1, 6, 12, and 24 months, and the women were seen at 6, 12, and 24 months. At follow-up, the cumulative incidence of HIV in wives of circumcised men was actually higher than that observed in the wives of the noncircumcised men, at 13.8 per 100 person-years compared with 9.6 per 100 person-years, respectively.

occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo were: **Cardiac Disorders**—palpitations; **Eye Disorders**—vision blurred; **Gastrointestinal Disorders**—nausea, dry mouth, diarrhea, constipation\*, abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain), vomiting; **General Disorders and Administration Site Conditions**—fatigue (includes asthenia); **Investigations**—weight decreased\*; **Metabolism and Nutrition Disorders**—decreased appetite (includes anorexia); **Nervous System Disorders**—dizziness, somnolence (includes hypersomnia and sedation), tremor; **Psychiatric Disorders**—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), anxiety, decreased libido (includes loss of libido), orgasm abnormal (includes anorgasmia), abnormal dreams (includes nightmare); **Reproductive System and Breast Disorders**—erectile dysfunction, ejaculation delayed, ejaculation disorder (includes ejaculation failure and ejaculation dysfunction); **Respiratory, Thoracic, and Mediastinal Disorders**—yawning; **Skin and Subcutaneous Tissue Disorders**—hyperhidrosis; **Vascular Disorders**—hot flush. \*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.

The most commonly observed adverse reactions in duloxetine-treated MDD/GAD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, constipation, somnolence, decreased appetite, and hyperhidrosis.

**Diabetic Peripheral Neuropathic Pain**—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPN placebo-controlled trials (N=225 Cymbalta 60 mg BID; N=228 Cymbalta 60 mg QD; N=115 Cymbalta 20 mg QD; N=223 placebo) with an incidence greater than placebo were: **Gastrointestinal Disorders**—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; **General Disorders and Administration Site Conditions**—fatigue, asthenia, pyrexia; **Infections and Infestations**—nasopharyngitis; **Metabolism and Nutrition Disorders**—decreased appetite, anorexia; **Musculoskeletal and Connective Tissue Disorders**—muscle cramp, myalgia; **Nervous System Disorders**—somnolence, headache, dizziness, tremor; **Psychiatric Disorders**—insomnia; **Renal and Urinary Disorders**—pollakiuria; **Reproductive System and Breast Disorders**—erectile dysfunction; **Respiratory, Thoracic and Mediastinal Disorders**—cough, pharyngolaryngeal pain; **Skin and Subcutaneous Tissue Disorders**—hyperhidrosis.

The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence  $\leq$  placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence  $\geq$ 5% and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

**Effects on Male and Female Sexual Function**—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, 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. Physicians should routinely inquire about possible sexual side effects. See Table 5 in full PI for specific ASEX results.

**Vital Sign Changes**—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure [see *Warnings and Precautions*].

Duloxetine treatment, for up to 13-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 beats per minute.

**Weight Changes**—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

**Laboratory Changes**—Cymbalta treatment in placebo-controlled clinical trials, 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*].

**Electrocardiogram Changes**—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13-weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of the corrected QT interval was observed.

**Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine**—Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 23,983 patients were treated with duloxetine. Of these, 6,702 took duloxetine for at least 6 months, and 3,006 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 and tachycardia; **Ear and Labyrinth Disorders**—*Frequent*: vertigo; *Infrequent*: ear pain and tinnitus; **Endocrine Disorders**—*Infrequent*: Hypothyroidism; **Eye Disorders**—*Frequent*: vision blurred; *Infrequent*: diplopia and visual disturbance; **Gastrointestinal Disorders**—*Frequent*: flatulence; *Infrequent*: eructation, gastritis, halitosis, and stomatitis; *Rare*: gastric ulcer, hematochezia, and melena; **General Disorders and Administration Site Conditions**—*Frequent*: chills/rigors; *Infrequent*: feeling abnormal, feeling hot and/or cold, malaise, and thirst; *Rare*: gait disturbance; **Infections and Infestations**—*Infrequent*: gastroenteritis and laryngitis; *Investigations*—*Frequent*: weight increased; *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 paresthesia/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**—*Infrequent*: dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal; **Reproductive System and Breast Disorders**—*Frequent*: anorgasmia/orgasm abnormal; *Infrequent*: menopausal symptoms, and sexual dysfunction; **Respiratory, Thoracic and Mediastinal Disorders**—*Frequent*: yawning; *Infrequent*: throat tightness; **Skin and Subcutaneous Tissue Disorders**—*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.

**Postmarketing Spontaneous Reports**—The following adverse reactions have been identified during postapproval 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 duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

**DRUG INTERACTIONS:** Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

**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*].

**Inhibitors of CYP2D6**—Concomitant use of duloxetine (40 mg QD) with paroxetine (20 mg QD) 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*].

**Dual Inhibition of CYP1A2 and CYP2D6**—Concomitant administration of duloxetine 40 mg BID 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  $C_{max}$ .

**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. These studies 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 coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued [see *Warnings and Precautions*].

**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.

**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.

**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, unopposed 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*].

**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 BID).

Although the difference between the two groups was not statistically significant and could be a product of chance, “we were not seeing a trend toward protection that we would have expected and hoped for,” Dr. Wawer said.

The researchers did observe that in both arms of the study, the incidence of HIV was highest in the first 6 months of follow-up and, in the circumcision arm specifically, the excess transmissions during this period occurred in couples who resumed intercourse more than 5 days before the circumcision wound was certified as fully healed, Dr. Wawer said.

“We’re still analyzing the data, but it ap-

pears that after 6 months there is a trend toward protection in the circumcision group.” This finding, she noted, stresses the importance of waiting to have sex until the circumcision wound is fully healed to minimize the risk of HIV transmission.

Reporting on another of the Rakai studies that looked at the efficacy of male circumcision in the prevention of herpes simplex virus type 2 (HSV-2) among HSV-2- and HIV-nega-

tive men, Dr. Aaron Tobian, also of Johns Hopkins, noted that the relative risk of HSV-2 acquisition among the 1,400 men randomized to immediate circumcision was 7.6%, compared with 10.1% in the 1,387 men randomized to delayed circumcision.

In a nested study comprising 825 wives of men in the circumcision arm and 783 wives of men in the control arm who were followed for 1 year, the respective

rates of symptomatic genitourinary disease in the intervention and control arms were 12.5% and 16.8%. The respective prevalence rates of trichomoniasis were 5.9% vs. 11.2%, and rates of bacterial vaginosis were 40.3% and 50.6%. Severe bacterial vaginosis was observed in 2.0% of the intervention wives and 6.5% of the control wives, Dr. Tobian said.

“HSV-2 infections, genital ulcer disease, and bacterial vaginosis are all cofactors for HIV infection,” he said.

By reducing the occurrence of these cofactors, “male circumcision offers some protection against HIV in these women,” he asserted. ■

### The finding stresses the importance of waiting to have sex until the circumcision wound is fully healed to minimize the risk of HIV transmission.

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

**Drugs Metabolized by CYP2C9**—Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

**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—Switching Patients to or from a Monoamine Oxidase Inhibitor**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI [see *Contraindications and Warnings and Precautions*].

**Serotonergic Drugs**—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs or tryptophan is not recommended [see *Warnings and Precautions*].

**Triptans**—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see *Warnings and Precautions*].

**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*].

**CNS Drugs**—[see *Warnings and Precautions*].

**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.

**USE IN SPECIFIC POPULATIONS: Pregnancy**—Teratogenic Effects, Pregnancy Category C—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 (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis 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 (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m<sup>2</sup> 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.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects**—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), 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 features are consistent with either a direct toxic effect of SSRIs and SNRIs 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*].

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

**Labor and Delivery**—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine

therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

**Pediatric Use**—Safety and effectiveness in the pediatric population have not been established [see *Boxed Warning and Warnings and Precautions*]. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

**Geriatric Use**—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPNP studies, no overall differences in safety or effectiveness were 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*].

**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 Insufficiency**—[see *Warnings and Precautions*].

**Severe Renal Impairment**—[see *Warnings and Precautions*].

**DRUG ABUSE AND DEPENDENCE: 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).

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

**OVERDOSAGE: 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.

**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.

**NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and 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 (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis) 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 (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m<sup>2</sup> basis) did not alter mating or fertility.

**PATIENT COUNSELING INFORMATION:** See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

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## Wisconsin Starts SCID Screening In Newborns

PHILADELPHIA — A neonatal screening test for severe combined immunodeficiency was added to Wisconsin's newborn screening panel Jan. 1, making it the first state to screen newborns for the disease.

Although the start-up cost for automating the test was high—requiring installation of \$500,000 worth of equipment—and running the test will cost Wisconsin about another \$400,000 each year, the anticipated saving in medical costs for treating a single infant who develops complications from severe combined immunodeficiency (SCID) is about \$2 million, Dr. William J. Grossman said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Screening for SCID also marks the first time that newborn screening has used a polymerase chain reaction-based (PCR-based) test. This step will likely pave the way for the eventual introduction of several more PCR-based tests into newborn screening, Dr. Grossman, a pediatrician at Children's Hospital of Wisconsin in Milwaukee, said in an interview.

Availability of an inexpensive, PCR-based screening test for SCID led to its being highlighted as a priority for newborn screening last year by the SCID Newborn Screening Working Group (J. Allergy Clin. Immunol. 2007;120:760-8). The group cited the clinical importance of intervening before an infant develops a first infection because of SCID, and the efficacy of treatment by stem-cell transplantation. The survival rate of infants with SCID who are not diagnosed or treated until after they are 3.5 months old is about 66%. That rate is about 96% if diagnosis and treatment occur before infants reach 3.5 months.

Pilot newborn screening done in Wisconsin last year identified a TREC (T-cell receptor-rearrangement excision circles) number of less than 75 per dried blood spot as a signal of SCID. The incidence of newborns who fell into this category was 0.02%. Pilot testing showed that this screen was able to pick up all four true positive SCID specimens that were introduced into the screened specimens. Specimens that screen positive are followed by a flow cytometry test to directly quantify T-cell numbers and confirm the SCID diagnosis.

—Mitchel L. Zoler