FLUOXETINE- fluoxetine capsule
DIRECT RX

FLUOXETINE

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [see WARNINGS AND PRECAUTIONS (5.1)].
In patients of all ages who are started on antidepressant therapy, monitor closely for worsening and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [seeWARNINGS AND PRECAUTIONS (5.1)].
Fluoxetine is not approved for use in children less than 7 years of age [see WARNINGS AND PRECAUTIONS (5.1) and USE IN SPECIFIC POPULATIONS (8.4)].
When using fluoxetine and olanzapine in combination, also refer to Boxed Warning section of the package insert for Symbyax.

hese highlights do not include all the information needed to use
see full prescribing information for
Initial U.S. Approval

As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility.

7.1 Monoamine Oxidase Inhibitors (MAOI)
[See DOSAGE AND ADMINISTRATION (2.9, 2.10), CONTRAINDICATIONS (4.1), and WARNINGS AND PRECAUTIONS (5.2)].

7.2 CNS Acting Drugs
Caution is advised if the concomitant administration of fluoxetine and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status [see CLINICAL PHARMACOLOGY (12.3)].

7.3 Serotonergic Drugs
[See DOSAGE AND ADMINISTRATION (2.9, 2.10), CONTRAINDICATIONS (4.1), and WARNINGS AND PRECAUTIONS (5.2)].

7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, 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 SNRIs or SSRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when fluoxetine is initiated or discontinued [see WARNINGS AND PRECAUTIONS (5.7)].

7.5 Electroconvulsive Therapy (ECT)
There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

7.6 Potential for Other Drugs to affect Fluoxetine

Drugs Tightly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma proteins, adverse effects may result from displacement of protein-bound fluoxetine by other tightly-bound drugs [see CLINICAL PHARMACOLOGY (12.3)].

7.7 Potential for Fluoxetine to affect Other Drugs

Pimozide — Concomitant use in patients taking pimozide is contraindicated. Pimozide can prolong the QT interval. Fluoxetine can increase the level of pimozide through inhibition of CYP2D6. Fluoxetine can also prolong the QT interval. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT prolongation warrants restricting the concurrent use of pimozide and fluoxetine [see CONTRAINDICATIONS (4.2), WARNINGS AND PRECAUTIONS (5.11), and DRUG INTERACTIONS (7.8)].

Thioridazine — Thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued, because of the risk of QT Prolongation [see CONTRAINDICATIONS (4.2), WARNINGS AND PRECAUTIONS (5.11), and DRUG INTERACTIONS (7.8)].

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25 mg oral dose of thioridazine produced a 2.4-fold higher Cmax and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine.

Thioridazine administration produces a dose-related prolongation of the QT interval, which is associated with serious ventricular arrhythmias, such as Torsades de Pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism.

Drugs Metabolized by CYP2D6 — Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued [see CONTRAINDICATIONS (4.2)].

Tricyclic Antidepressants (TCAs) — In 2 studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCAs may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued [see WARNINGS AND PRECAUTIONS (5.2) and CLINICAL PHARMACOLOGY (12.3)].

Benzodiazepines — The half-life of concurrently administered diazepam may be prolonged in some patients [see CLINICAL PHARMACOLOGY (12.3)]. Coadministration of alprazolam and fluoxetine has

resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Antipsychotics — Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine.

Anticonvulsants — Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Lithium — There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly [see WARNINGS AND PRECAUTIONS (5.2)].

Drugs Tightly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma proteins, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect [see CLINICAL PHARMACOLOGY (12.3)].

Drugs Metabolized by CYP3A4 — In an in vivo interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine.

Additionally, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Olanzapine — Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

When using fluoxetine and olanzapine and in combination, also refer to the Drug Interactions section of the package insert for Symbyax.

7.8 Drugs that Prolong the QT Interval

Do not use fluoxetine in combination with thioridazine or pimozide. Use fluoxetine with caution in combination with other drugs that cause QT prolongation. These include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, mesoridazine, droperidol); specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin); Class 1A antiarrhythmic medications (e.g., quinidine, procainamide); Class III antiarrhythmics (e.g., amiodarone, sotalol); and others (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus). Fluoxetine is primarily metabolized by CYP2D6. Concomitant treatment with CYP2D6 inhibitors can increase the concentration of fluoxetine. Concomitant use of other highly protein-bound drugs can increase the concentration of fluoxetine [see CONTRAINDICATIONS (4.2), WARNINGS AND PRECAUTIONS (5.11), DRUG INTERACTIONS (7.7), and CLINICAL PHARMACOLOGY (12.3)].

When using fluoxetine and olanzapine in combination, also refer to the Use in Specific Populations section of the package insert for Symbyax.

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C — Fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a background risk of birth defects, loss, or

other adverse outcome regardless of drug exposure.

Treatment of Pregnant Women during the First Trimester — There are no adequate and well-controlled clinical studies on the use of fluoxetine in pregnant women. Results of a number of published epidemiological studies assessing the risk of fluoxetine exposure during the first trimester of pregnancy have demonstrated inconsistent results. More than 10 cohort studies and case-control studies failed to demonstrate an increased risk for congenital malformations overall. However, one prospective cohort study conducted by the European Network of Teratology Information Services reported an increased risk of cardiovascular malformations in infants born to women (N = 253) exposed to fluoxetine during the first trimester of pregnancy compared to infants of women (N = 1359) who were not exposed to fluoxetine. There was no specific pattern of cardiovascular malformations. Overall, however, a causal relationship has not been established.

Nonteratogenic Effects — Neonates exposed to fluoxetine and other 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 (5.2)].

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiological studies suggest a positive statistical association between SSRI use (including fluoxetine) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with fluoxetine, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. The decision can only be made on a case by case basis [see DOSAGE AND ADMINISTRATION (2.7)].

Animal Data — In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of fluoxetine at doses up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times, respectively, the maximum recommended human dose (MRHD) of 80 mg on a mg/m2 basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m2 basis).

8.2 Labor and Delivery

The effect of fluoxetine on labor and delivery in humans is unknown. However, because fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse effects on the newborn, fluoxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Because fluoxetine is excreted in human milk, nursing while on fluoxetine is not recommended. In one breast-milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

8.4 Pediatric Use

Use of fluoxetine in children - The efficacy of fluoxetine for the treatment of Major Depressive Disorder was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤18 [see CLINICAL STUDIES (14.1)].

The efficacy of fluoxetine for the treatment of OCD was demonstrated in one 13-week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to <18 [see CLINICAL STUDIES (14.2)].

The safety and effectiveness in pediatric patients <8 years of age in Major Depressive Disorder and <7 years of age in OCD have not been established.

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤18) with Major Depressive Disorder or OCD [see CLINICAL PHARMACOLOGY (12.3)].

The acute adverse reaction profiles observed in the 3 studies (N=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse reaction profile observed in the 19-week Major Depressive Disorder study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine [see ADVERSE REACTIONS (6.1)].

Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients. Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the acute phases of the 3 studies combined. Consequently, regular monitoring for the occurrence of mania/hypomania is recommended.

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height and 1.1 kg less in weight than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine [see WARNINGS AND PRECAUTIONS (5.6)].

Fluoxetine is approved for use in pediatric patients with MDD and OCD [see BOX WARNING and WARNINGS AND PRECAUTIONS (5.1)]. Anyone considering the use of fluoxetine in a child or adolescent must balance the potential risks with the clinical need.

Animal Data - Significant toxicity on muscle tissue, neurobehavior, reproductive organs, and bone development has been observed following exposure of juvenile rats to fluoxetine from weaning through maturity. Oral administration of fluoxetine to rats from weaning postnatal day 21 through

adulthood day 90 at 3, 10, or 30 mg/kg/day was associated with testicular degeneration and necrosis, epididymal vacuolation and hypospermia (at 30 mg/kg/day corresponding to plasma exposures [AUC] approximately 5 to 10 times the average AUC in pediatric patients at the MRHD of 20 mg/day), increased serum levels of creatine kinase (at AUC as low as 1 to 2 times the average AUC in pediatric patients at the MRHD of 20 mg/day), skeletal muscle degeneration and necrosis, decreased femur length/growth and body weight gain (at AUC 5 to 10 times the average AUC in pediatric patients at the MRHD of 20 mg/day). The high dose of 30 mg/kg/day exceeded a maximum tolerated dose. When animals were evaluated after a drug-free period (up to 11 weeks after cessation of dosing), fluoxetine was associated with neurobehavioral abnormalities (decreased reactivity at AUC as low as approximately 0.1 to 0.2 times the average AUC in pediatric patients at the MRHD and learning deficit at the high dose), and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose). In addition, the testicular and epididymal microscopic lesions and decreased sperm concentrations found in high dose group were also observed, indicating that the drug effects on reproductive organs are irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed.

These fluoxetine toxicities in juvenile rats have not been observed in adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving 3, 10, or 30 mg/kg/day doses in this study are approximately 0.1 to 0.2, 1 to 2, and 5 to 10 times, respectively, the average exposure in pediatric patients receiving the MRHD of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, are approximately 0.3 to 0.8, 1 to 8, and 3 to 20 times, respectively, the pediatric exposure at the MRHD.

A specific effect on bone development was reported in juvenile mice administered fluoxetine by the intraperitoneal route to 4 week old mice for 4 weeks at doses 0.5 and 2 times the oral MRHD of 20 mg/day on mg/m2 basis. There was a decrease in bone mineralization and density at both doses, but the overall growth (body weight gain or femur length) was not affected.

Use of fluoxetine in combination with olanzapine in children and adolescents: Safety and efficacy of fluoxetine and olanzapine in combination in patients 10 to 17 years of age have been established for the acute treatment of depressive episodes associated with Bipolar I Disorder. Safety and effectiveness of fluoxetine and olanzapine in combination in patients less than 10 years of age have not been established.

8.5 Geriatric Use

U.S. fluoxetine clinical trials included 687 patients ≥65 years of age and 93 patients ≥75 years of age. The efficacy in geriatric patients has been established [see CLINICAL STUDIES (14.1)]. For pharmacokinetic information in geriatric patients [see CLINICAL PHARMACOLOGY (12.4)]. 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. SNRIs and SSRIs, including fluoxetine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction [see WARNINGS AND PRECAUTIONS (5.9)].

Clinical studies of olanzapine and fluoxetine in combination did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose of fluoxetine should be used in patients with cirrhosis. Caution is advised when using fluoxetine in patients with diseases or conditions that could affect its metabolism [see DOSAGE AND ADMINISTRATION (2.7) and CLINICAL PHARMACOLOGY (12.4)].

9.3 Dependence

Fluoxetine has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with fluoxetine did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited 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 history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of fluoxetine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

10.1 Human Experience

Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdosage, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdosage were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was nonlethal.

Other important adverse reactions reported with fluoxetine overdose (single or multiple drugs) include coma, delirium, ECG abnormalities (such as nodal rhythm, QT interval prolongation and ventricular arrhythmias, including Torsades de Pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like reactions, pyrexia, stupor, and syncope.

10.2 Animal Experience

Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose [see OVERDOSAGE (10.3)].

10.3 Management of Overdose

For current information on the management of fluoxetine overdose, contact a certified poison control

center (1-800-222-1222 or www.poison.org). Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multi-drug overdose.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use general supportive and symptomatic measures. Induction of emesis is not recommended.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known.

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation [see DRUG INTERACTIONS (7.7)].

For specific information about overdosage with olanzapine and fluoxetine in combination, refer to the Overdosage section of the Symbyax package insert.

Fluoxetine capsules, USP are a selective serotonin reuptake inhibitor for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem®, fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)oxy]propylamine hydrochloride and has the molecular formula of C17H18F3NO•HCl. Its molecular weight is 345.79. The structural formula is:

Chemical Structure

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each capsule contains fluoxetine hydrochloride equivalent to 10 mg (32.3 µmol), 20 mg (64.7 µmol), or 40 mg (129.3 µmol) of fluoxetine. The capsules also contain the following inactive ingredients: colloidal silicon dioxide, FD&C Blue #1, gelatin, pregelatinized starch (maize), sodium lauryl sulphate, titanium dioxide and yellow iron oxide. In addition 40 mg also contains FD&C Yellow #6. The capsules are printed with edible ink containing black iron oxide, potassium hydroxide, propylene glycol, shellac and strong ammonia solution.

12.1 Mechanism of Action
Although the exact mechanism of fluoxetine is unknown, it is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin.

12.2 Pharmacodynamics
Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

12.3 Pharmacokinetics
Systemic Bioavailability — In man, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.

The capsule and oral solution dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food.

Protein Binding — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of

fluoxetine is bound in vitro to human serum proteins, including albumin and α1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important.

Enantiomers — Fluoxetine is a racemic mixture (50/50) of R-fluoxetine and S-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The S-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Metabolism — Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, S-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to R- or S-fluoxetine. R-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Variability in Metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-norfluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine’s metabolism, like that of a number of other compounds including TCAs and other selective serotonin reuptake inhibitors (SSRIs), involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions [see DRUG INTERACTIONS (7.7)].

Accumulation and Slow Elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used [see WARNINGS AND PRECAUTIONS (5.14)]. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine’s metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

12.4 Specific Populations

Liver Disease — As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This suggests that the use

of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used [see DOSAGE AND ADMINISTRATION (2.7), USE IN SPECIFIC POPULATIONS (8.6)].

Renal Disease — In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Geriatric Pharmacokinetics — The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse reactions was observed in those elderly patients.

Pediatric Pharmacokinetics (children and adolescents) — Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with Major Depressive Disorder or Obsessive Compulsive Disorder (OCD). Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children were 2-fold higher than in adolescents (171 and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 8 to <18) diagnosed with Major Depressive Disorder.

Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity — The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively [approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose (MRHD) of 80 mg on a mg/m2 basis], produced no evidence of carcinogenicity.

Mutagenicity — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility — Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m2 basis) indicated that fluoxetine had no adverse effects on fertility. However, adverse effects on fertility were seen when juvenile rats were treated with fluoxetine [see USE IN SPECIFIC POPULATIONS (8.4)].

13.2 Animal Toxicology and/or Pharmacology

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

Fluoxetine Capsules USP, 20 mg* are opaque green cap/opaque off white body, size ‘3’ hard gelatin

capsule filled with white to off-white granular powder and imprinted with ‘E’ on opaque green cap and ‘91’ on opaque off white body with black ink.

Fluoxetine Capsules, USP

(floo ox' e teen)

Read the Medication Guide that comes with fluoxetine capsules before you start taking them and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about fluoxetine capsules?

Fluoxetine capsules and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

Fluoxetine capsules and other antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment or when the dose is changed.
Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
Watch for these changes and call your healthcare provider right away if you notice:
New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
Pay particular attention to such changes when fluoxetine capsules are started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:

attempts to commit suicide
acting on dangerous impulses
acting aggressive or violent
thoughts about suicide or dying
new or worse depression
new or worse anxiety or panic attacks
feeling agitated, restless, angry or irritable
trouble sleeping
an increase in activity or talking more than what is normal for you
other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. Fluoxetine capsules may be associated with these serious side effects:

2. Serotonin Syndrome. This condition can be life-threatening and may include:

agitation, hallucinations, coma or other changes in mental status
coordination problems or muscle twitching (overactive reflexes)
racing heartbeat, high or low blood pressure
sweating or fever
nausea, vomiting, or diarrhea
muscle rigidity
dizziness

flushing
tremor
seizures

3. Severe allergic reactions:

trouble breathing
swelling of the face, tongue, eyes or mouth
rash, itchy welts (hives) or blisters, alone or with fever or joint pain

4. Abnormal bleeding: Fluoxetine capsules and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.

5. Visual Problems:

eye pain
changes in vision
swelling or redness in or around the eye
Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

6. Seizures or convulsions

7. Manic episodes:

greatly increased energy
severe trouble sleeping
racing thoughts
reckless behavior
unusually grand ideas
excessive happiness or irritability
talking more or faster than usual

8. Changes in appetite or weight. Children and adolescents should have height and weight monitored during treatment.

9. Low salt (sodium) levels in the blood. Elderly people may be at greater risk for this. Symptoms may include:

headache
weakness or feeling unsteady
confusion, problems concentrating or thinking or memory problems

10. Changes in the electrical activity of your heart (QT prolongation and ventricular arrhythmia including Torsades de Pointes). This condition can be life threatening. The symptoms may include:

fast, slow, or irregular heartbeat
shortness of breath
dizziness or fainting

Do not stop fluoxetine capsules without first talking to your healthcare provider. Stopping fluoxetine capsules too quickly may cause serious symptoms including:

anxiety, irritability, high or low mood, feeling restless or changes in sleep habits
headache, sweating, nausea, dizziness
electric shock-like sensations, shaking, confusion

What are fluoxetine capsules?

Fluoxetine capsules are a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider.

Fluoxetine capsules are used to treat:

Major Depressive Disorder (MDD)
Obsessive Compulsive Disorder (OCD)
Bulimia Nervosa*
Panic Disorder*
Depressive episodes associated with Bipolar I Disorder, taken with olanzapine (Zyprexa)

* Not approved for use in children

Talk to your healthcare provider if you do not think that your condition is getting better with fluoxetine capsules treatment.

Who should not take fluoxetine capsules?

Do not take fluoxetine capsules if you:

are allergic to fluoxetine hydrochloride or any of the ingredients in fluoxetine capsules. See the end of this Medication Guide for a complete list of ingredients in fluoxetine capsules.
take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
Do not take an MAOI within 5 weeks of stopping fluoxetine capsules unless directed to do so by your physician.
Do not start fluoxetine capsules if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

People who take fluoxetine capsules close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:

high fever
uncontrolled muscle spasms
stiff muscles
rapid changes in heart rate or blood pressure
confusion
loss of consciousness (pass out)

take Mellaril® (thioridazine). Do not take Mellaril® within 5 weeks of stopping fluoxetine capsules because this can cause serious heart rhythm problems or sudden death.
take the antipsychotic medicine pimozide (Orap®) because this can cause serious heart problems.

What should I tell my healthcare provider before taking fluoxetine capsules? Ask if you are not sure.

Before starting fluoxetine capsules, tell your healthcare provider if you:

Are taking certain drugs or treatments such as:
Triptans used to treat migraine headache
Medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium,

buspirone, SSRIs, SNRIs, MAOIs or antipsychotics
Tramadol and fentanyl
Over-the-counter supplements such as tryptophan or St. John's Wort
Electroconvulsive therapy (ECT)
have liver problems
have kidney problems
have heart problems
have or had seizures or convulsions
have bipolar disorder or mania
have low sodium levels in your blood
have a history of a stroke
have high blood pressure
have or had bleeding problems
are pregnant or plan to become pregnant. It is not known if fluoxetine capsules will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy.
are breast-feeding or plan to breast-feed. Some fluoxetine may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking fluoxetine capsules.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Fluoxetine capsules and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take fluoxetine capsules with your other medicines. Do not start or stop any medicine while taking fluoxetine capsules without talking to your healthcare provider first.

If you take fluoxetine capsules, you should not take any other medicines that contain fluoxetine hydrochloride including:

Symbyax
Sarafem
How should I take fluoxetine capsules?
Take fluoxetine capsules exactly as prescribed. Your healthcare provider may need to change the dose of fluoxetine capsules until it is the right dose for you.
Fluoxetine capsules may be taken with or without food.
If you miss a dose of fluoxetine capsules, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of fluoxetine capsules at the same time.
If you take too much fluoxetine call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking fluoxetine capsules?

Fluoxetine capsules can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how fluoxetine capsules affect you. Do not drink alcohol while using fluoxetine capsules.

What are the possible side effects of fluoxetine capsules?

Fluoxetine capsules may cause serious side effects, including:

See "What is the most important information I should know about fluoxetine capsules?"
Problems with blood sugar control. People who have diabetes and take fluoxetine capsules may have problems with low blood sugar while taking fluoxetine capsules. High blood sugar can happen when fluoxetine capsules are stopped. Your healthcare provider may need to change the dose of your diabetes medicines when you start or stop taking fluoxetine capsules.

Feeling anxious or trouble sleeping

Common possible side effects in people who take fluoxetine capsules include:

unusual dreams
sexual problems
loss of appetite, diarrhea, indigestion, nausea or vomiting, weakness, or dry mouth
flu symptoms
feeling tired or fatigued
change in sleep habits
yawning
sinus infection or sore throat
tremor or shaking
sweating
feeling anxious or nervous
hot flashes
rash

Other side effects in children and adolescents include:

increased thirst
abnormal increase in muscle movement or agitation
nose bleed
urinating more often
heavy menstrual periods
possible slowed growth rate and weight change. Your child's height and weight should be monitored during treatment with fluoxetine capsules.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of fluoxetine capsules. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store fluoxetine capsules?

Store fluoxetine capsules at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).
Keep fluoxetine capsules away from light.
Keep fluoxetine capsules bottle closed tightly.

Keep fluoxetine capsules and all medicines out of the reach of children.

General information about fluoxetine capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use fluoxetine capsules for a condition for which it was not prescribed. Do not give fluoxetine capsules to other people, even if they have the same condition. They may harm them.

This Medication Guide summarizes the most important information about fluoxetine capsules. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about fluoxetine capsules that is written for healthcare professionals.

For more information about fluoxetine capsules, call Aurobindo Pharma USA, Inc. at 1-866-850-2876.

What are the ingredients in fluoxetine capsules?

Active ingredient: fluoxetine hydrochloride

Inactive ingredients: colloidal silicon dioxide, FD&C Blue #1, gelatin, pregelatinized starch (maize), sodium lauryl sulphate, titanium dioxide and yellow iron oxide. In addition 40 mg also contains FD&C Yellow #6. The capsules are printed with edible ink containing black iron oxide, potassium hydroxide, propylene glycol, shellac and strong ammonia solution.

Symbyax® and Sarafem® are registered trademarks of Eli Lilly and Company.
Mellaril® is a registered trademark of Novartis AG Corporation.
Orap® is a registered trademark of Teva Pharmaceuticals USA.
Coumadin® is a registered trademark of Bristol Myers Squibb.
Jantoven® is a registered trademark of Upsher-Smith Laboratories Inc.
Zyprexa® is a registered trademark of Eli Lilly and Company.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Dispense with Medication Guide available at: www.aurobindousa.com/product-medication-guides

FLUOXETINE

fluoxetine capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-869(NDC:65862-193)

Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FLUOXETINE HYDROCHLORIDE (UNII: I9W7N6B1KJ) (FLUOXETINE - UNII:01K63SUP8D)	FLUOXETINE	20 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
STARCH, CORN (UNII: O8232NY3SJ)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
GELATIN (UNII: 2G86QN327L)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
AMMONIA (UNII: 5138Q19F1X)	
SHELLAC (UNII: 46N107B71O)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	green (Opaque Green) , white (Opaque Off white)	**Score**	score with uneven pieces
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	E;91
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:61919-869-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	10/25/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078619	10/25/2016	

Labeler - DIRECT RX (079254320)

Registrant - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations

DIRECT RX		079254320	repack(61919-869)