EXHIBIT 35
NolvaDex—Cont.

Acute overdose in humans has not been reported. In a study of advanced metastatic cancer patients which specifically determined the maximum tolerated dose of NOLVADEX in evaluating the use of very high doses to reverse multi-drug resistance, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness was noted. One patient experienced a seizure several days after NOLVADEX was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to NOLVADEX therapy is unknown. Doses given in these patients were all greater than 400 mg/day. In a single patient, NOLVADEX was given twice a day. In the same study, prolongation of the QT interval on the electrocardiogram was noted when patients were given doses higher than 250 mg/day, leading dose, followed by maintenance of 80 mg/day of NOLVADEX given twice a day. For a woman with a body surface area of 1.6 m² the minimum loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 6 fold higher in respect to the maximum recom- mended dose.

Specific treatment for overdose is not available; treatment must be symptomatic.

**DOSE AND ADMINISTRATION**

For patients with breast cancer, the recommended daily dose is 20–40 mg. Doses greater than 20 mg per day should be given in divided doses (morning and evening).

**How Supplied**

20 mg Tablets containing tamoxifen as the citrate in an oral solution, biconvex, round, white tablets identified with NOLVADEX 604 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. NDC: 0010-0500-26

20 mg Tablets containing tamoxifen as the citrate in an oral solution, biconvex, round, white tablets identified with NOLVADEX 604 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 30 tablets. NDC: 0010-0600-26

Store at controlled room temperature, 20–25°C (68–77°F) [see USP]. Dispense in a well-closed, light-resistant container.

**Pharmacokinetics**

Quetiapine fumarate is a white to off-white crystalline powder. It is freely soluble in water. SEROQUEL is supplied for oral administration as 25 mg (peach), 100 mg (yellow) and 200 mg (white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

**Clinical Pharmacology**

**Pharmacodynamics**

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain; serotonin 5HT2A and 5HT2C (IC50 >100 nM), dopamine D2 and 5HT2 receptors (IC50 >5 nM), histamine H1, (IC50 >300 nM), and adrenergic a1 and a2 receptors (IC50 >10 nM). SEROQUEL has a preferential affinity at choleserin muscarinic and benzodiazepine receptors (IC50 >5000 nM).

The mechanism of action of SEROQUEL, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin 5-HT2A (5HT2A) receptor antagonism. Other than dopamine and 5HT2 receptor antagonism, other studies have shown that SEROQUEL may have a number of effects on the serotonin and dopaminergic systems.

In three short-term (6-week) controlled trials involving elderly patients (mean age 65 years, n=9) compared to young patients (mean age 20±10 years, n=8) had a 25% lower bioavailability of quetiapine compared to young patients.

**Interactions**

**Drug:Drug Interactions**

In in vitro inhibition studies, SEROQUEL showed moderate inhibition of the CYP3A4 enzyme. Dose adjustment of SEROQUEL may be necessary if it is co-administered with drugs and, phenytoin. Dose adjustment of SEROQUEL will be necessary if it is co-administered with lamotrigine.

**Drug:Drug Interactions**

SEROQUEL is indicated in the management of the manifestations of psychotic disorders was established in 3 short-term (6-week) controlled trials of psychotic inpatients who received the medication as a single daily dose. The fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose was chosen to provide a reliable and valid comparison with the SEROQUEL data. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the heptatically impaired population, and dosage adjustment may be necessary.

**Clinical Efficacy Data**

SEROQUEL in the management of the manifestations of psychotic disorders was established in 3 short-term (6-week) controlled trials of psychotic inpatients who received the medication as a single daily dose. The fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose was chosen to provide a reliable and valid comparison with the SEROQUEL data. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the heptatically impaired population, and dosage adjustment may be necessary.

**Several instruments were used for assessing psychiatric symptoms and side effects in these studies, among them the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression (CGI), and the Hamilton Depression Rating Scale (HAMD) for depression. The Clinical Global Impression (CGI). reflects the impression of a skilled observer, fully familiar with the manifestations of schizoaffective disorder, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.**

(1) In a 6-week, placebo-controlled trial (n=363) involving 5 fixed doses of SEROQUEL (0.75, 1.5, 3.0, 6.0, and 7.5 mg/ day), the BPRS total score, the CGI severity score, and the CGI overall improvement score showed a dose-related decrease. The effectiveness of SEROQUEL group (mean dose, 600 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. A second traditional assessment; the Clinical Global Improvement (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms. **(2) In a 6-week, placebo-controlled trial (n=286) involving 5 fixed doses of SEROQUEL (0.75, 1.5, 3.0, 6.0, and 7.5 mg/ day), the BPRS total score, the CGI severity score, and the CGI overall improvement score showed a dose-related decrease. The effectiveness of SEROQUEL group (mean dose, 600 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. A second traditional assessment; the Clinical Global Improvement (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms. **(3) In a 6-week, placebo-controlled trial (n=286) involving 5 fixed doses of SEROQUEL (0.75, 1.5, 3.0, 6.0, and 7.5 mg/ day), the BPRS total score, the CGI severity score, and the CGI overall improvement score showed a dose-related decrease. The effectiveness of SEROQUEL group (mean dose, 600 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. A second traditional assessment; the Clinical Global Improvement (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms. **(4) In a 6-week, placebo-controlled trial (n=286) involving 5 fixed doses of SEROQUEL (0.75, 1.5, 3.0, 6.0, and 7.5 mg/ day), the BPRS total score, the CGI severity score, and the CGI overall improvement score showed a dose-related decrease. The effectiveness of SEROQUEL group (mean dose, 600 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. A second traditional assessment; the Clinical Global Improvement (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms. **(4) In a 6-week, placebo-controlled trial (n=286) involving 5 fixed doses of SEROQUEL (0.75, 1.5, 3.0, 6.0, and 7.5 mg/ day), the BPRS total score, the CGI severity score, and the CGI overall improvement score showed a dose-related decrease. The effectiveness of SEROQUEL group (mean dose, 600 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. A second traditional assessment; the Clinical Global Improvement (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.
QULONG for extended periods should periodically and for the first 3 to 8 weeks of treatment for the treatment of manic symptoms in patients with bipolar I disorder whose manic symptoms were inadequately controlled with concomitant mood stabilizers and/or other antipsychotics. After the initial 3 to 8 weeks, the recommended dosage level should be continued for at least 12 weeks, unless clinical response has been adequate and maintenance treatment is not warranted. If the dosage level is increased, a gradual increase is recommended. It is advisable to have the patient's weight monitored before starting treatment with SEEROQUEL and at times during treatment.

SIDE EFFECTS

Patients treated with SEEROQUEL have experienced adverse effects that may be related to the antipsychotic drug class and may include extrapyramidal symptoms (EPS), including dystonia, tardive dyskinesia, akathisia, or acute dystonic reactions. Therefore, the following information should be read carefully by both the patient and the prescriber before initiating treatment with SEEROQUEL:

1. Extrapyramidal symptoms (EPS): EPS include a variety of motor symptoms such as akathisia, dystonia, akinesia, and extrapyramidal drug-induced movement disorders. EPS may occur at any time during treatment with SEEROQUEL, including during the initial phase of therapy, when the dosage is increased or when the dosage is decreased. EPS may occur in patients of all ages, including children and elderly patients. EPS are more likely to occur in patients who are elderly and in those who have a history of neurologic illness. EPS may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. EPS may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

2. Tardive dyskinesia: Tardive dyskinesia (TD) is a movement disorder that occurs primarily in children and elderly patients. TD may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. TD is more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. TD may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

3. Monitoring for extrapyramidal symptoms and tardive dyskinesia: Patients with extrapyramidal symptoms and tardive dyskinesia should be monitored regularly in the hospital and outpatient setting. If extrapyramidal symptoms or tardive dyskinesia occur, the patient should be treated with a benzodiazepine or other antipsychotic drug. If the extrapyramidal symptoms or tardive dyskinesia continue, the dosage of SEEROQUEL should be decreased or the drug should be discontinued.

4. Neuroleptic malignant syndrome (NMS): NMS is a serious, potentially life-threatening syndrome that occurs most frequently in association with the use of antipsychotic drugs. NMS may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. NMS may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. NMS may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

5. Aspiration pneumonia: Aspiration pneumonia is a complication of antipsychotic drug therapy. Aspiration pneumonia may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. Aspiration pneumonia may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. Aspiration pneumonia may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

6. Diaphoresis: Diaphoresis may be associated with the use of antipsychotic drugs. Diaphoresis may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. Diaphoresis may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. Diaphoresis may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

7. Body temperature regulation: Body temperature regulation is a complication of antipsychotic drug therapy. Body temperature regulation may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. Body temperature regulation may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. Body temperature regulation may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

8. Drug interactions: Drug interactions are a complication of antipsychotic drug therapy. Drug interactions may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. Drug interactions may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. Drug interactions may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

9. Hepatic toxicity: Hepatic toxicity is a complication of antipsychotic drug therapy. Hepatic toxicity may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. Hepatic toxicity may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. Hepatic toxicity may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

10. Prolactin elevation: Prolactin elevation is a complication of antipsychotic drug therapy. Prolactin elevation may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. Prolactin elevation may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. Prolactin elevation may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

11. Teratogenicity: Teratogenicity is a complication of antipsychotic drug therapy. Teratogenicity may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. Teratogenicity may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. Teratogenicity may be more likely to occur in patients who have a history of neurologic illness or who are elderly.

12. Pregnancy: Pregnancy may be a complication of antipsychotic drug therapy. Pregnancy may be more likely to occur in patients who are elderly and in those who have a history of neurologic illness. Pregnancy may also be more likely to occur in patients who receive high doses of SEEROQUEL or who have a history of alcohol abuse or substance abuse. Pregnancy may be more likely to occur in patients who have a history of neurologic illness or who are elderly.
Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A inhibitors: Although data are not available from clinical studies with quetiapine, quetiapine is metabolized by a P450 3A enzyme (e.g., iraconazole, itraconazole, fluconazole, and ketoconazole).

Hydroxylation: Iloprost, Imipramine, Haloperidol, and Risperidone: Coadministration of iloprost (60 ng once daily); imipramine (75 mg bid), haloperidol (3 mg bid), or risperidone (3 mg bid) with quetiapine did not have any effect on the steady state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs: Lorcaserin: The minimum therapeutic dose of lorcaserin (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg bid dosing. Lithium: The clearance of quetiapine (250 mg tid) with lithium had no effect on any of the steady state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day of antipyrine (metabolized by P450 2C19 enzyme) to subjects with selected psychiatric disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites in vivo. Antipyrine metabolism in vivo does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Camoginerine, Metagennine, Impairment of Fertility: Cardiopacemaker studies in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg or in rats at doses of 20, 60, and 240 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (500 mg/kg) on a mg/m² basis. Drug-related effects included increases in human dose on a mg/m² basis (rats). There were statistically significant increases in thyroid gland follicular ad¬

soemases in male mice at doses of 500 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose (250 mg/kg) in female rats at doses of 250 mg/kg or 3.0 times the maximum human dose on a mg/m² basis. Mammary gland adenocarcinomas were increased in female rats at a dose of 150 mg/kg (0.6 times the maximum human dose on a mg/m² basis). A sample menstrual cycle of 28 days was observed in female rats at all doses tested (25, 75, 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m² basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormones (TSH) resulting from enhanced metabolism of thyroid hormone by quetiapine. The clearance of thyroid hormone was reduced in rats treated with quetiapine (34%). The clearance of total T3 and T4 was not affected. The clearance of T4 was increased by 50% in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antidepressants. The relevance of the results of these studies are not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk is unknown (see Hyperprolactinemia in PHARMACOTHERAPY).

Mutagenesis: The mutagenic potential of quetiapine was tested in six in vitro bacterial gene mutation assays and in an in vitro micronuclear assay for sister chromatid exchange in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tested strains. Quetiapine did not induce micronuclei in one Salmonella typhimurium test strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an in vitro chromosomal aberration assay with Chinese Hamster Embryo cells. Quetiapine was not mutagenic in the micronucleus assay in rats. Impairment of Fertility: Quetiapine decreased mating and fertility in male F344 rats dosed at 15-100 mg/kg for 2 weeks or 100 mg/kg for 2 weeks. These doses are equivalent to 0.3 to 2.4 times the maximum human dose on a mg/m² basis. It is ass?ciated with a mean increase in heart rate, as determined while receiving therapy following baseline evaluation.

Consequences of the increased incidence of greater than 5% in any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials: Dose Dependency Events: Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300, 600 mg, and 750 mg/ day) to placebo were explored for dose-relatedness of adverse events. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or more in patients treated with SEROQUEL but not in placebo) were tremor, somnolence, and hyperprolactinemia. In particular, tremor, somnolence, and hyperprolactinemia were more common in the premarketing experience for SEROQUEL suggested that it is associated with a mean increase in heart rate, as determined while receiving therapy following baseline evaluation.
SEROQUEL is a list of COSTART terms that reflect treat- ments observed during the premarketing experience of SEROQUEL. It is important to emphasize that, although adverse events are categorized by body system and listed in decreasing frequency according to the following order: system frequent adverse events are those occurring in 1/100 patients (those not already listed in the ad) results from placebo-controlled trials appear in italics; infrequent adverse events are those occurring 1/1000 patients; rare events are those occurring in < 1/1000 patients.

### System:

- **Frequency:** Frequent: hypotension, dysuria; Infrequent: abdominal dreams, dyskinesia, thinking abnormal, dyskinesia, vertigo, involuntary movements, confusia, psychosis, hallucinations, hyperkinesia, Li-crest ed urinary retention, incoordination, paranoïd, an normal grief, myoclonus, delusions, manic reac- tivity, ataxia, depersonalization, stupor, bruxism, cata- reaction, hemiplegia; Rare: aphasia, buccoglossal pa, chorea, choreothetosis, delirium, emotional lability, es, libidoe decreased*, neuralgia, stuttering, subconjugal.

### as a Whole:

- **Frequency:** Frequent: flu syndrome; Infrequent: sin, pelvic pain*, suicide attempt, malaise, photoex- reaction, chills face edema, moniliasis; Rare: abdo- malgia.

### IV System:

- **Frequency:** Frequent: anorexia; Infrequent: in- dol salivation, increased appetite, gustna glutamin seritalize increased, gingivitis, dyspnea, flatulence, enteritis, gastritis, hemorrhoids, stomatitis, thirst, caries, fecal incontinence, gastroparesis reflex, emesis, mouth ulceration, rectal hemorrhage, a edema; Rare: glottitis, hematemesis, intestinal ob- tion, mesna, pancreatitis.

### CNS System:

- **Frequency:** Frequent: palpitation; Infrequent: ilation, QT interval prolonged, migraines, bradycar- rebral ischemia, irregular pulse, T wave abnormality, + branch; Rare: cerebrovascular accident, deep phobeblips, T wave inversion; Rare: angina pectoris, fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

### Respiratory System:

- **Frequency:** pharyngitis, rhinitis, cough increased, dyspncea; Infrequent: pneumonia, epi- staxis; Rare: hiccup, hyperventilation.

### Metabolic and Nutritional System:

- **Frequency:** peripheral edema; Infrequent: weight loss, alkaline phosphatase in- creased, hypolipidemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; Rare: gly- cerca, goit, hand edema, hypokalemia, water intoxica- tion.

### Skin and Appendages System:

- **Frequency:** sweating; Infre- quent: pruritus, acne, eczema, contact dermatitis, maculo- papular rash, pruritus, skin ulcer; Rare: exfoliative derma- titis, psoriasis, skin discolouration.

### Urogenital System:

- **Frequency:** dysmenorrhea*, vagini- te, urinary incontinence, micturition*, impotence*, dys- uria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation, leu­korrhoe*, vaginal hemorrhage*, vaginovaginitis*; Rare: gynecomastia*, nocturia, polynu, acute kidney failure.

### Special Senses:

- **Frequency:** conjunctivitis, abnormal vi- nion, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; Rare: abnormality of accommodation, deafness, glau- coma.

### Musculoskeletal System:

- **Frequency:** pathologic frac- tures, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

### Hemic and Lymphatic System:

- **Frequency:** leukopenia; Infrequent: leukocytosis, antigen, eosinophilia, hypercholesterolemia, lymphadenopathy, cyanosis; Rare: hir- molysis, thrombocytopenia.

### Endocrine System:

- **Frequency:** hypothyroidism, diabetes mellitus; Rare: hyperthyroidism.

- **Adjusted for gender**

### DRUG ABUSE AND DEPENDENCE

- **Controled Substance Class:** SEROQUEL is not a controlled substance.

### Physical and Psychologic dependence:

- **SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence.**

- **While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this lim- ited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Conse­quently, patients should be evaluated carefully for a his­tory of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., develop­ment of tolerance, increases in dose, drug-seeking behavior.

### Table 1. Treatment-Emergent Adverse Experience

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* Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, chest pain; is accidental tolerated, to a target dose range of 400 mg daily. In clinical trials, increases in dose increments of 225 mg bid were generally well tolerated. Above 600 mg daily, treatment-emergent adverse events, including those already listed in Table 1, were infrequent, as were laboratory abnormalities. In one controlled trial (225 mg bid) was also effective.

### OVERDOSE

- **Human experience:** Experience with SEROQUEL (quetiapine fumarate) in acute overdose was limited in the clinical trial database (27 reported doses ranging from 1200 mg to 9500 mg and 9 fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the effects of the drug's known pharmacological properties, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypotension, bradycardia, and/or seizures.

- **Management of Overdose:** In case of acute overdose, establish and maintain an airway and ensure adequate ox­ ygenation and ventilation. Gastric decontamination is recommended (if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtaining, sedation or dyskinesia of the head and neck following overdose may create a risk of aspira­tion with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhyth­mias. If arrhythmogenic rhythm is administered, dis­opyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects. These constraints in patients with acute overdose of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quet­iapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be considered. The possibility of multiple drug involvement should be consid­ered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopa­mine) should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In case of severe cardiovascular decompensation or/and cholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

### DOSAGE AND ADMINISTRATION

- **Usual Dose:** SEROQUEL should generally be administered with an initial dose of 35 mg bid, with increases in increments of 50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage ad­justment, if considered, should be carried out in increments of not less than 2 days, as steady state for SEROQUEL would not be achieved for approximately 1–2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25–50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

### Antipsychotic efficacy was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effective­ness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400–500 mg/day appear to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

### Steering in Special Populations

- **Consideration should be given to a slower rate of dose titra­tion and a lower target dose in the elderly, in patients with hepatic impairment, and in patients who are of older or who had a predisposition to hyponatremic reactions (see CLINICAL PHARMACOLOGY). When indicated, dose es­kalation should be performed with caution in these patients. The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is concomitantly administered with phenytoin and other enzyme inducers such as carbamazepine and pheno­barbital. (See Drug Interactions under PRECAUTIONS) Maintenance Treatment: While there is no body of evidence available to answer the question of how long a patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic agents. It is recommended that re­spending patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for main­tenance treatment.

### Reinduction of Treatment in Patients Previously Discontin­ued

- **Although there are no clinical studies specifically designed to address reinduction of treatment, it is recommended that when re-starting patients who have had an interval of less than one week of SEROQUEL, titration of SEROQUEL should be re­quired, and the maintenance dose may be re-established. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.**

### Switching from Other Antipsychotics: There are no sys­tematically collected data to specifically address switching from other antipsychotics to SEROQUEL.

**Continued on next page**

Consult 1993 PDR® supplements and future editions for revisions
Seroquel—Cont.

HOW SUPPLIED
25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SERQUEL' and '25' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SERQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SERQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F) excursions permitted to 15°C–50°F (59–90°F). [See USP]

ANIMAL TOXICOLOGY
Quetiapine produced a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10–250 mg/kg in rats, 75–750 mg/kg in mice. The maximum recommended human dose (on a mg/kg basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional significance and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 8 or 12 months, but not for 1 month, focal triangular ataracts occurred at the junction of posterior estheses in the plane of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/kg basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of ataracts in individual dogs. The appearance of delta-4-cholesterol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species.

In a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 217 females at a dose of 225 mg/kg. This side effect was not seen in males at this dose. In another study, 214 females at a dose of 100 mg/kg did not show this side effect. In a 2-year toxicity study in rats, the occurrence of posterior sutures in the outer cortex of the lens was observed in a special sub-group of 141 females at a dose of 100 mg/kg. The occurrence of this effect exceeds rotation of +134° (c = 1.0, P = .001). This side effect was not seen in males at this dose. In a 2-year toxicity study in monkeys, a striated appearance of the anterior lens surface was detected in 217 females at a dose of 225 mg/kg. This side effect was not seen in males at this dose.

Sorbitrate® CHEWABLE TABLETS USP

Sorbitrate® CHEWABLE TABLETS USP are available as:

- 5 mg Chewable Tablets
- 10 mg Chewable Tablets

Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch, yellow 10. [See USP]

Sorbitrate® ORAL TABLETS USP

Sorbitrate® ORAL TABLETS USP are available as:

- 5 mg Oral Tablet
- 10 mg Oral Tablet

Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch, yellow 10.

5 mg Oral Tablet: Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch, yellow 10.

10 mg Oral Tablet: Each tablet contains 10 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch, yellow 10.

5 mg Chewable Tablet: Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch, yellow 10.

10 mg Chewable Tablet: Each tablet contains 10 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose monohydrate, magnesium stearate, pregelatinized starch, yellow 10.

Sorbitrate® CHEWABLE TABLETS USP 5 mg Chewable Tablets have a bitter taste. Absorption of isosorbide dinitrate after oral dosing is nearly complete, but bioavailability is highly variable (10%–90%). With extensive first-pass metabolism in the liver, serum levels of ISDN reach their maxima about an hour after ingestion. Isosorbide dinitrate is known to be nearly complete, but bioavailability is highly variable.

Ketoconazole and other similar drugs can increase plasma concentrations of isosorbide dinitrate by competitive inhibition of the CYP3A4 isozyme. The concomitant use of ketoconazole and ISDN requires careful monitoring for ISDN-related side effects.

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must be used to avoid the hazards of hypoten- sion and cyanida. Because the effects of oral and chewable ISDN dos are so difficult to terminate rapidly, this formulation of recommendations in these settings.

ECATIONS

Severe hypotension, particularly with upri- ght, may occur with even small doses of isosorbide dini- rate. This drug should therefore be used with caution in indi- cations for which there is no other acceptable alternative.

It is advisable to begin therapy in a recumbent or seated position. This was comparable to that observed in breathlessness despite adequate oxygen delivery in these settings.

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PHARMACOLOGY

The oral isosorbide dinitrate is an extended release tablet dosage form that produces the desired effect. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activity as a vasodilator is not decreased by hypotension or a nurse- ling infant. The desired dose (LD50) was found to be 1100 mg/kg when administered orally. In rabbits, the oral isosorbide dinitrate's activ...