

IOM Backs Medicare Shift to Pay for Performance

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The U.S. Department of Health and Human Services should gradually replace Medicare's current payment system with a pay-for-performance system that would reward physicians and other providers for efficiency along with patient-centered, quality care, according to a report from the Institute of Medicine. Pay-for-performance plans do not yet

have an established track record of improving care, so IOM's report, "Rewarding Provider Performance: Aligning Incentives in Medicare," urges a phased-in program that will evaluate pay-for-performance initiatives as they are implemented.

Pay for performance will help transform the Medicare payment system into one that rewards both higher value and better outcomes, Robert Reischauer, Ph.D., president of the Washington-based Urban Institute, said at a press briefing

sponsored by IOM. Dr. Reischauer served on the committee that wrote the report.

"The committee does not feel that pay for performance is the magic bullet," he said. "Pay for performance should be considered one of several key elements needed to restructure the current payment system."

Any changes in Medicare's payment system would need Congressional approval.

The panel's report urged lawmakers to adopt an initial system that would reduce

base Medicare payments across the board and use the money to fund rewards for strong performance. At the same time, Medicare officials would evaluate the program to make certain it is having the desired effects.

The proportion of Medicare payment withheld would be small at first, and providers would be compensated both for excellent work and for improving performance in areas that encompass care quality, efficiency, and "patient centeredness."

"We are recommending a performance-based system in which both excellence is rewarded and significant improvement is rewarded," Dr. Reischauer said. "Everyone can play and everyone can get back the money that was withheld initially from them."

Many large health care providers and organizations could participate in a Medicare pay-for-performance system and should be required to do so as soon as it is launched, the IOM report said. But par-

BRIEF SUMMARY of Prescribing Information—Before prescribing, please consult complete Prescribing Information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seven placebo-controlled trials (total duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appear to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

INDICATIONS AND USAGE: Bipolar Mania: SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunctive therapy to lithium or divalproex. The efficacy of SEROQUEL in acute bipolar mania was established in one 12-week monotherapy trial and one 3-week adjunctive therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunctive therapy. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. **Schizophrenia:** SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL (quetiapine) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning). **Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reinitiation of drug treatment should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dysrhythmic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask or temporarily suppress the syndrome. The effect that symptoms have upon the long-term course of the syndrome is unknown. When these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest doses and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome. **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspected drug.

PRECAUTIONS: General: Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-escalation period, probably reflecting its α_1 -adrenergic antagonist properties. Syncope was reported in 1% (2/2057) of the patients treated with SEROQUEL compared with 0% (0/607) on placebo and about 0.4% (2/527) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose to hypotension (eg, dehydration, orthostatic hypotension, and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **Cataracts:** The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lens-related effects cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment. **Seizures:** During clinical trials, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. **Cardiac Effects:** Conditions that may increase the risk of torsades de pointes are more prevalent in a population of 65 years or older. Hypothetical: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of T4 were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 15% (12/731) of SEROQUEL patients did not receive TSH increases in monitoring studies. SEROQUEL treatment should be discontinued if a patient with a hypothyroidism diagnosis requires replacement thyroid treatment. In the mainia adjunct studies, where SEROQUEL was added to lithium or divalproex, 12% (24/196) of SEROQUEL-treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL-treated patients with elevated TSH, 3 had simultaneous low free T4 levels. **Cholesterol and Triglyceride Elevations:** In schizophrenia trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to increases in weight observed in SEROQUEL-treated patients. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of $>$ 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of $>$ 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL, especially during the 3-5 day period of initial dose-escalation. In schizophrenia trials, somnolence was reported in 19% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunctive therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Wrist pain:** One case of wrist pain in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce wrist pain, and it is possible that SEROQUEL may share this capacity. Severe pruritus may require surgical intervention. **Body Temperature Regulation:** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may

contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance:** Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be cautioned of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be advised of the potential for impaired judgment, thinking, or motor skills, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should be advised not to breast feed if they are taking SEROQUEL. **Concomitant Medication:** As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs. **Alcohol:** Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL. **Heat Exposure and Dehydration:** Patients should be advised regarding avoiding overheating and dehydration. **Anticholinergics:** Patients should be advised that laboratory tests are recommended. **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of other antihypertensive agents such as operating a motor vehicle (including automobiles) and operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **The Effect of Other Drugs on Quetiapine:** Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (eg, carbamazepine, barbiturates, rifampin, glaucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, valproate). **Divalproex:** Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine by 17% without affecting the pharmacokinetics of divalproex. **Other Drugs:** Cimetidine (250 mg tid) and ranitidine (150 mg tid) increased the mean oral clearance of quetiapine by 65%. **Carbamazepine:** Administration of multiple daily doses of cimetidine (400 mg qd for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg bid). Dose adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 35% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (eg, itraconazole, fluconazole, and erythromycin). **Fluoxetine, Imipramine, Thioridazine:** Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg qd for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg bid). Dose adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 35% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (eg, itraconazole, fluconazole, and erythromycin). **Fluoxetine, Imipramine, Thioridazine:** Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg qd for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg bid). Dose adjustment for quetiapine is not required when it is given with cimetidine. **Pharmacokinetics:** Quetiapine is rapidly absorbed and reaches its maximum plasma concentration (C_{max}) within 1 hour. The mean oral clearance of quetiapine (150 mg bid) was 1.5 and 4.5 times the maximum human dose on a mg/m² basis (rats) and 250 and 750 mg/day, respectively, in male and female rats. There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m² basis, respectively. There were no statistically significant increases in thyroid gland follicular adenomas in female mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m² basis, respectively. There were statistically significant increases in mammary gland adenocarcinomas in male mice at doses of 250 mg/kg or 3.0 times the maximum human dose on a mg/m² basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 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 hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in rats. In a rat and mouse study of the relationship between thyroid gland adenomas to human risk, through whatever mechanism, is unknown. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-year toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 3- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are not considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to humans is unknown. **Mutagenesis:** The mutagenic potential of quetiapine was tested in *in vitro* bacterial gene mutation assays and in an *in vivo* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats. **Impairment of Fertility:** Quetiapine decreased mating and fertility in male Sprague-Dawley rats at doses of 50 and 150 mg/kg or 0.5 and 1.5 times the maximum human dose on a mg/m² basis. Drug-related effects included increases in female to male and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m² basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at a dose of 50 mg/kg, or 0.5 times the maximum human dose on a mg/m² basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m² basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m² basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Beagle dogs during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m² basis or in rabbits at 25 to 100 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m² basis. There were, however, evidence of embryonic lethality, fetal loss, and resorptions in rats and rabbits at 10, 100 and 200 mg/kg or 0.1, 0.12, and 0.24 times the maximum human dose on a mg/m² basis. In a preliminary preclinical study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of SEROQUEL on labor and delivery in humans is unknown. **Nursing Mothers:** SEROQUEL was excreted in milk of lactating animals during lactation studies. It is not known whether SEROQUEL is excreted in human milk. Caution should be taken when SEROQUEL should not be breast fed. **Pediatric Use:** The safety and effectiveness of SEROQUEL in pediatric patients have not been established. **Geriatric Use:** Of the approximately 3400 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostatic effects should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients. **ADVERSE REACTIONS:** The information below is derived from a clinical trial database for SEROQUEL consisting of over 3000 patients. This database includes 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunctive therapy) and approximately 2600 patients on normal doses exposed to 1 to 3 or one dose of SEROQUEL for the treatment of schizophrenia. Of these approximately 3000 subjects, approximately 2700 (2200 in schizophrenia and 405 in acute bipolar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 5143 patients. Refer to the full Prescribing Information for details of adverse event data collection. **Adverse Findings Observed in Short-Term, Controlled Trials: Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials: Bipolar Mania:** Overall, discontinuations due to adverse events were 5.7% for SEROQUEL vs. 5.1% for placebo in monotherapy and 6.6% for SEROQUEL vs. 5.9% for placebo in adjunctive therapy. **Schizophrenia:** Overall, there was no difference in the incidence of adverse events between SEROQUEL vs. 3% for placebo in monotherapy in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see PRECAUTIONS). Somnolence 0.8% vs 0% for placebo and hypotension 0.4% vs 0% for placebo. **Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials:** The prescriber should be aware that the figures in the tables and tabulations in the full Prescribing Information cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, users, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence in the population studied. **Table 1, in the full Prescribing Information, enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.**

Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials* for the Treatment of Schizophrenia and Bipolar Mania (monotherapy): Body as a Whole: Headache, Pain, Asthenia, Abdominal Pain, Back Pain, Fever, Cardiovascular: Tachycardia, Postural Hypotension; Digestive: Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl, Transpeptidase Increased; Metabolic and Nutritional: Weight Gain, S/GPT Increased, S/GOT Increased; Nervous: Agitation, Somnolence, Dizziness, Anxiety, Respiratory: Pharyngitis, Rhinitis; Skin and Appendages: Rash; Special Senses: Amblyopia. *Events for which the SEROQUEL incidence was equal to or less than placebo are not listed, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hyperreflexia, hypertensive crisis, hypotension, insomnia, leukopenia, malaise, nausea, nervousness, paraesthesia, peripheral edema, sweating, tremor, and weight loss. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), S/GPT increased (5%), weight gain (5%), and dyspepsia (5%). Table 2, from the full Prescribing Information, enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunctive therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. **Treatment-Emergent Adverse Experience Incidence in 3-Week, Placebo-Controlled Clinical Trials* for the Treatment of Bipolar Mania (Adjunctive Therapy): Body as a Whole:** Headache, Asthenia, Abdominal Pain, Back Pain, Cardiovascular: Postural Hypotension; Digestive: Dry Mouth, Constipation; Metabolic and Nutritional: Weight Gain; Nervous: Somnolence, Dizziness, Tremor, Agitation; Respiratory: Pharyngitis. *Events for which the SEROQUEL incidence was equal to or less than placebo are not listed, but included the following: akathisia, diarrhea, insomnia, and nausea. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%). Explorations for interactions on the basis of gender, age, and race did not reveal 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-Related Adverse Events:** Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-related adverse events. Logistic regression analyses revealed a positive dose response ($p < 0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain. **Extrapyramidal Symptoms:** Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous completion of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hyperreflexia, hyperkinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. **Vital Signs and Laboratory Studies: Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see PRECAUTIONS). **Weight Gain:** In schizophrenia trials the proportions of patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunctive therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in S/GPT and increases in both total cholesterol and triglycerides (see PRECAUTIONS). An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo. **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QTc, QT, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.3% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania adjunctive therapy trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see PRECAUTIONS). **Other Adverse Events Observed During the Pre-Marketing Evaluation for SEROQUEL:** Following is a list of COASTAR terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was not identified, and those event terms which were so general as to be uninformative. It is important to emphasize that although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Nervous System:** Involuntary: hypertonia, dysarthria; **Intraque:** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased; **urinary retention, incontinence, paranoid delusion, abnormal gait, myoclonus, delusions, mania, reaction, apathy, akathia, depersonalization, bipolar disorder, cataplexy, depression, hemiparesis; Rare:** acute kidney failure, acute renal failure, choreoathetosis, delirium, emotional lability, euphoria, libido decreased, neuralgia, slurring, subacute hemorrhage. **Body as a Whole:** Involuntary: hypertonia, dysarthria; **Intraque:** neck pain, pelvic pain, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; **Rare:** abdominal angery; **Digestive System:** frequent: anorexia; **Intraque:** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; **Rare:** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. **Cardiovascular System:** frequent: palpitation; **Intraque:** vasodilation, QT interval prolonged, myocardial, bradycardia, cerebral ischemia, irregular pulse, 1 wave inversion; **Rare:** abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** angina pectoris, atrial fibrillation, AV block, first degree congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. **Respiratory System:** frequent: pharyngitis, rhinitis, cough increased, dyspnea; **Intraque:** pneumonia, epistaxis, asthma; **Rare:** hiccup, hyperventilation. **Metabolic and Nutritional System:** frequent: peripheral edema; **Intraque:** weight loss, alkaline phosphatase increased, hyperkalemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; **Rare:** glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System:** frequent: sweating; **Intraque:** pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; **Rare:** exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System:** frequent: dysmenorrhea; **Rare:** urinary incontinence, metrorrhagia, impotence; **dysuria, vaginal moniliasis; abnormal ejaculation; cystitis, urinary frequency, amenorrhea; female lactation; Rare:** abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** acute kidney failure, acute renal failure, choreoathetosis, delirium, emotional lability, euphoria, libido decreased, neuralgia, slurring, subacute hemorrhage. **Body as a Whole:** frequent: flu-like syndrome; **Intraque:** neck pain, pelvic pain, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; **Rare:** abdominal angery; **Digestive System:** frequent: increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; **Rare:** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. **Cardiovascular System:** frequent: palpitation; **Intraque:** vasodilation, QT interval prolonged, myocardial, bradycardia, cerebral ischemia, irregular pulse, 1 wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** angina pectoris, atrial fibrillation, AV block, first degree congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. **Respiratory System:** frequent: pharyngitis, rhinitis, cough increased, dyspnea; 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