

# Hospitalists Urged to Act as 'Agents of Change'

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VANCOUVER, B.C. — Hospitalists are ideally qualified and positioned to drive hospital quality improvement initiatives, Dr. Larry Wellikson said at the annual Canadian Hospitalist Conference.

"We are owners, not renters," he said, contrasting hospitalists with house staff and other physicians. Not only do hospitalists know their institutions inside and

out, they often have more clout to effect change than do allied health professionals. And hospitalists are intrinsically involved in overarching issues of care, such as drug safety and patient education.

Hospital care today leaves much room for improvement, Dr. Wellikson said.

"We are virtually the only industry where you pay exactly the same thing whether you get the worst care or the best care." Moreover, limited measurement of quality outcomes makes it diffi-

cult to compare the caliber of care across hospitals.

The Society of Hospital Medicine has taken a leading role in supporting hospitalists in working to change the status quo, according to Dr. Wellikson, CEO of the society.

The many guidelines for standards of care that have been written are merely an initial step in quality improvement (QI), and implementation is a key focus of SHM, he said. The society has brought to-

gether multidisciplinary groups of experts to create virtual resource rooms on its Web site ([www.hospitalmedicine.org](http://www.hospitalmedicine.org)) that provide tools for use by hospitalists involved in QI projects.

In addition, because physicians seldom learn how to conduct QI projects during their medical education, the society offers QI training at its annual and chapter meetings, Dr. Wellikson noted.

SHM also has defined core competencies for hospital care and secured funding

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In these trials, sedation was reported in 30% of patients on SEROQUEL compared to 8% 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. **Priapism** One case of priapism 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 priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism 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, e.g., 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. In 2 eight-week clinical studies in patients with bipolar depression (N=1048) the incidence of treatment emergent suicidal ideation or suicide attempt was low and similar to placebo (SEROQUEL 300 mg, 6/350, 1.7%; SEROQUEL 600 mg, 9/348, 2.6%; Placebo, 7/347, 2.0%). **Use in Patients with Concomitant Illness** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited [see **Pharmacokinetics** in full Prescribing Information (12.3)]. 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 **Warnings and Precautions**). **Withdrawal** Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including SEROQUEL. Gradual withdrawal is advised.

### ADVERSE REACTIONS

**Clinical Study Experience** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The information below is derived from a clinical trial database for SEROQUEL consisting of over 4300 patients. This database includes 698 patients exposed to SEROQUEL for the treatment of bipolar depression, 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy), 646 patients exposed to SEROQUEL for the maintenance treatment of bipolar I disorder as adjunct therapy, and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia. Of these approximately 4300 subjects, approximately 4000 (2300 in schizophrenia, 405 in acute bipolar mania, 698 in bipolar depression, and 646 for the maintenance treatment of bipolar I disorder) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 2400 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reaction categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse reactions for schizophrenia and bipolar mania. MedDRA terminology has been used to classify reported adverse reactions for bipolar depression. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials Bipolar Disorder:** Depression: Overall, discontinuations due to adverse reactions were 12.3% for SEROQUEL 300 mg vs. 19.0% for SEROQUEL 600 mg and 5.2% for placebo. **Mania:** Overall, discontinuations due to adverse reactions were 5.7% for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy. **Schizophrenia:** Overall, there was little difference in the incidence of discontinuation due to adverse reactions (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **Warnings and Precautions**).

Adverse Reaction	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

**Adverse Reactions 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 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, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied. Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions 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.

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**Table 2. Treatment-Emergent Adverse Reaction Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)<sup>1</sup>**

Body System/ Preferred Term	SEROQUEL (n=719)	PLACEBO (n=404)
<b>Body as a Whole</b>		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal Pain	4%	1%
Back Pain	3%	1%
Fever	2%	1%
<b>Cardiovascular</b>		
Tachycardia	6%	4%
Postural Hypotension	4%	1%
<b>Digestive</b>		
Dry Mouth	9%	3%
Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%
Gastroenteritis	2%	0%
Gamma Glutamyl Transpeptidase Increased	1%	0%
<b>Metabolic and Nutritional</b>		
Weight Gain	5%	1%
SGPT Increased	5%	1%
SGOT Increased	3%	1%
<b>Nervous</b>		
Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%
<b>Respiratory</b>		
Pharyngitis	4%	3%
Rhinitis	3%	1%
<b>Skin and Appendages</b>		
Rash	4%	2%
<b>Special Senses</b>		
Amblyopia	2%	1%

<sup>1</sup> Reactions for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

In these studies, the most commonly observed adverse reactions 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%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%). Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions 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 adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

**Table 3. Treatment-Emergent Adverse Reaction Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)<sup>1</sup>**

Body System/ Preferred Term	SEROQUEL (n=196)	PLACEBO (n=203)
<b>Body as a Whole</b>		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
<b>Cardiovascular</b>		
Postural Hypotension	7%	2%
<b>Digestive</b>		
Dry Mouth	19%	3%
Constipation	10%	5%
<b>Metabolic and Nutritional</b>		
Weight Gain	6%	3%
<b>Nervous</b>		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
<b>Respiratory</b>		
Pharyngitis	6%	3%

<sup>1</sup> Reactions for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.

to pursue mentored implementation projects, whereby hospitalist leaders trained in QI mentor others involved in projects to improve quality outcomes. One project, conducted at a University of California, San Diego, hospital, led to a near doubling of the rate of adequate prophylaxis for venous thromboembolism and reduced the annual number of venous thromboembolic events from 50 to 4, he said.

SHM also is leading efforts to set standards for transitions of care at hospital admission and discharge, in part because hospitalists have often been criticized as contributing to a lack of continuity of care, according to Dr. Wellikson.

The society's long-term strategy for QI includes an emphasis on teamwork and efforts to bring together allied health professionals, Dr. Wellikson explained at the conference, which was sponsored by the University of British Columbia.

"We need to move toward a world where health care is a team sport," he said, noting that empowering nurses, pharmacists, and other profes-



sionals can have benefits all around.

Dr. Wellikson cautioned against pursuing an illusion of improvement in place of the real thing. "The idea of a bunch of people running around with clipboards satisfying some regulations that will grow from 10 to 20 to 100 is really not having a culture of quality," he said. SHM is also evaluating how information technology can best be harnessed to support QI, and

**'You need to look at performance improvement as part of your DNA, as part of your job.'**

DR. WELLIKSON

evaluating how information technology can best be harnessed to support QI, and

is seeking to raise funds for research on the best ways to conduct QI.

He urged hospitalists not to view QI as a burdensome task undertaken at the end of the day. "You need to look at performance improvement as part of your DNA, as part of your job, as the gift or the differentiator that you bring to the marketplace," he advised. "It isn't that [others don't] care about quality or performance—it's just that you have the opportunity to seize this, own this, and be the agents of change."

Dr. Wellikson reported that he had no conflicts of interest in association with his presentation. ■

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In these studies, the most commonly observed adverse reactions 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%). Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 8 weeks) of bipolar depression in 5% or more of patients treated with SEROQUEL (doses of 300 and 600 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

patients meeting the same weight gain criterion were 8% compared to 2% for placebo. **Laboratory Changes** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides. In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed (see **Warnings and Precautions**). In placebo controlled monotherapy clinical trials involving 3368 patients on quetiapine fumarate and 1515 on placebo, the incidence of at least one occurrence of neutrophil count  $<1.0 \times 10^9/L$  among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine fumarate, compared to 0.1% (2/1349) in patients treated with placebo. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors (see **Warnings and Precautions**). **Hyperglycemia** In 2 long-term placebo-controlled clinical trials, mean exposure 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level ( $\geq 126$  mg/dl) for patients more than 8 hours since a meal was 18.0 per 100 patient years for SEROQUEL (10.7% of patients) and 9.5 for placebo per 100 patient years (4.6% of patients). In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with SEROQUEL and 1490 treated with placebo), the percent of patients who had a fasting blood glucose  $\geq 126$  mg/dl or a non fasting blood glucose  $\geq 200$  mg/dl was 3.5% for quetiapine and 2.1% for placebo. In a 24 week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level  $\geq 200$  mg/dl was 1.7% and the incidence of a fasting treatment-emergent blood glucose level  $\geq 126$  mg/dl was 2.6%. **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 QT, QTc, 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 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patients had heart rate increases to  $> 120$  beats per minute. 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 **Warnings and Precautions**). **Other Adverse Reactions Observed During the Pre-Marketing Evaluation of SEROQUEL** Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses  $\geq 75$  mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported reactions are included except those already listed in the tables or elsewhere in labeling, those reactions for which a drug cause was remote, and those reaction terms which were so general as to be uninformative. It is important to emphasize that, although the reactions reported occurred during treatment with SEROQUEL, they were not necessarily caused by it. Reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions 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 reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. **Nervous System: Frequent:** hypertonia, dysarthria; **Infrequent:** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased\*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; **Rare:** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased\*, neuralgia, stuttering, subdural hematoma. **Body as a Whole: Frequent:** flu syndrome; **Infrequent:** neck pain, pelvic pain\*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; **Rare:** abdomen enlarged. **Digestive System: Frequent:** anorexia; **Infrequent:** 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; **Infrequent:** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave 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; **Infrequent:** pneumonia, epistaxis, asthma; **Rare:** hiccup, hyperventilation. **Metabolic and Nutritional System: Frequent:** peripheral edema; **Infrequent:** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; **Rare:** glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System: Frequent:** sweating; **Infrequent:** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; **Rare:** exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System: Frequent:** dysmenorrhea\*, vaginitis\*, urinary incontinence, metrorrhagia\*, impotence\*, dysuria, vaginal moniliasis\*, abnormal ejaculation\*, cystitis, urinary frequency, amenorrhea\*, female lactation\*, leukorrhea\*, vaginal hemorrhage\*, vulvovaginitis\* orchitis\*; **Rare:** gynecomastia\*, nocturia, polyuria, acute kidney failure. **Special Senses: Frequent:** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; **Rare:** abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System: Frequent:** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. **Hemic and Lymphatic System: Frequent:** leukopenia; **Infrequent:** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; **Rare:** hemolysis, thrombocytopenia. **Endocrine System: Frequent:** hypothyroidism, diabetes mellitus; **Rare:** hyperthyroidism. **Post Marketing Experience** The following adverse reactions were identified during post approval of SEROQUEL. Because these

**Table 4. Treatment-Emergent Adverse Reaction Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression<sup>1</sup>**

Body System/ Preferred Term	SEROQUEL (n=698)	PLACEBO (n=347)
<b>Gastrointestinal Disorders</b>		
Dry Mouth	44%	13%
Constipation	10%	4%
Dyspepsia	7%	4%
Vomiting	5%	4%
<b>General Disorders and Administrative Site Conditions</b>		
Fatigue	10%	8%
<b>Metabolism and Nutrition Disorders</b>		
Increased Appetite	5%	3%
<b>Nervous System Disorders</b>		
Sedation	30%	8%
Somnolence	28%	7%
Dizziness	18%	7%
Lethargy	5%	2%
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Nasal Congestion	5%	3%

<sup>1</sup> Reactions for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, and headache.

In these studies, the most commonly observed adverse reactions 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 dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%). Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse reaction occurrence on the basis of these demographic factors. **Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials Dose-Related Adverse Reactions:** Spontaneously elicited adverse reaction 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-relatedness of adverse reactions. Logistic regression analyses revealed a positive dose response ( $p < 0.05$ ) for the following adverse reactions: dyspepsia, abdominal pain, and weight gain. **Adverse Reactions in Clinical Trials with Quetiapine and Not Listed Elsewhere in the Label:** The following adverse reactions have also been reported with quetiapine: abnormal dreams and nightmares, hypersensitivity, restless legs syndrome, and elevations in serum creatine phosphokinase (not associated with NMS). **Extrapyramidal Symptoms: Dystonia Class Effect:** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups. 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 complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

Dose Groups	SEROQUEL					
	Placebo	75 mg	150 mg	300 mg	600 mg	750 mg
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic medications	14%	11%	10%	8%	12%	11%

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse reactions potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups. **Vital Signs and Laboratory Studies Vital Sign Changes** SEROQUEL is associated with orthostatic hypotension (see **Warnings and 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 adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of

\* adjusted for gender