January 04, 2008

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Your Pharmaceutical Sales Specialist, b(6), has forwarded your request for information regarding SEROQUEL® (quetiapine fumarate) Tablets and SEROQUEL XR™ (quetiapine fumarate) Extended-Release Tablets. The following information is attached for your review:

- **SEROQUEL-Use for Major Depressive Disorder (MDD)**
- **SEROQUEL XR-Use for Major Depressive Disorder (MDD)**

The attached information is supplied to you as a professional courtesy in response to your request. It is intended to provide pertinent data to assist you in forming your own conclusions and making decisions. Prescription drugs used outside of their approved indication may not be eligible for reimbursement by any third-party payors, including Medicaid, Medicare, or similar federal or state programs. AstraZeneca does not recommend the use of SEROQUEL or SEROQUEL XR in any other manner than as described in the enclosed prescribing information.

Thank you for your interest in SEROQUEL® (quetiapine fumarate) Tablets and SEROQUEL XR™ (quetiapine fumarate) Extended-Release Tablets. If we may be of further assistance to you, please contact AstraZeneca at 1-800-236-9933.

Sincerely,

Frederick W. Kohler Jr., R.Ph., Ph.D.

Senior Medical Information Manager

INQ 635407

Tel 800 236 9933
Fax 302 885 1400
www.astrazeneca-us.com

Medical Resources FOC/CE1, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437

SEROQUEL-Use for Major Depressive Disorder (MDD)

Summary

- A double-blind, randomized, placebo-controlled study evaluated the use of combination quetiapine + fluoxetine vs. placebo + fluoxetine in major depression (MDD).[2] Ninety patients (78.9%) had a ≥50% reduction in their Montgomery-Asberg Depression Rating Scale (MADRS) score at least once during the 8 weeks of therapy; however, a difference in response was not found on the MADRS score between the quetiapine + fluoxetine group and the placebo + fluoxetine groups at week 8.
- A double-blind, placebo-controlled study evaluated the use of quetiapine as an adjunct to selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) for major depression.[3] Significant improvements from baseline were seen in Hamilton Rating Scale for Depression (HAM-D) at week 1 and at week 8 in the quetiapine vs. placebo groups. Most common reasons for study withdrawal included adverse events in the quetiapine group (n=8) and inefficacy in the placebo group (n=9).
- An 8-week, double-blind, randomized, placebo-controlled trial investigated the adjunct use of quetiapine in patients with a primary diagnosis of major depression and partially responsive to of SSRI/SNRI treatment.[4] HAM-D-17 scores significantly improved from baseline (25.0 vs. 24.5) to endpoint (8.3 vs. 14.7) in the quetiapine vs. placebo groups, respectively ($p<0.01$).
- A study evaluated the effectiveness of adding quetiapine to existent paroxetine therapy for the treatment of anxiety associated with depression.[5] The absolute decrease in the HAM-D score was significantly greater for the paroxetine + quetiapine group compared to paroxetine only group during the whole study period. "Increased appetite" was reported in 20.4% of the paroxetine + quetiapine group at week 6 which differed significantly from the 2.4% reported in the paroxetine only group; no other significant between-group differences were reported in the frequency of other adverse events
- Additional randomized and open-label studies examining quetiapine as adjunct therapy for MDD are summarized below.

Prescribing Information[1]

SEROQUEL is a psychotropic agent belonging to the dibenzothiazepine chemical class.

Indications

SEROQUEL is indicated for the treatment of:

- depressive episodes associated with bipolar disorder..
- acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex.
- schizophrenia.

Boxed Warning

***Suicidality and Antidepressant Drugs* — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in pediatric patients. (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use).**

SEROQUEL is not indicated for the treatment of major depressive disorder (MDD). Please see the enclosed SEROQUEL Prescribing Information for complete product information.

Clinical Data

Randomized, Controlled Studies

Martinez and colleagues[2] conducted an 8-week, double-blind, randomized, placebo-controlled trial comparing quetiapine + fluoxetine with placebo + fluoxetine. Outpatients (n=114; 51 males with a mean age of 40.7 years and 63 females with a mean age of 41.9 years) with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* MDD were included. Fluoxetine was initiated at 20 mg/day during weeks 1-4 and either 20 or 40 mg/day during weeks 5-8. Quetiapine was initiated at 25 mg/day and could be flexibly dosed, based on the patient response, to a maximum of 100 mg/day (in increments of 25 mg/day every third day). The primary outcome measure was the time to achieve a ≥50% reduction in baseline MADRS score. The mean MADRS score at baseline was 30.1.

A difference in response was not found on the MADRS score between the quetiapine + fluoxetine group and the placebo + fluoxetine groups at week 8. Ninety patients (78.9%) had a ≥50% reduction in their MADRS score at least once during the 8 weeks of therapy. Sixty-eight patients (59.6%) maintained response at week 8; 17 patients (14.9%) were non-responders. Twenty-nine patients dropped out of the study before week 8. A significant difference between groups in the Clinical Global Impressions (CGI)-Efficacy scores was seen at week 1 (p=0.005) and week 2 (p=0.04), but not at subsequent weeks. Patients in the quetiapine + fluoxetine group did not respond to treatment or show improvement from baseline in the Hamilton Anxiety Scale (HAM-A), CGI-Severity (CGI-S), or CGI-Improvement (CGI-I) scores any sooner than the placebo + fluoxetine group. The quetiapine + fluoxetine group improved more rapidly than the placebo + fluoxetine group in MADRS insomnia scores from baseline to the first follow-up

(p=0.00055), second follow-up (p=0.0004), and third follow-up (p=0.01). There were no significant differences between treatment groups in any of the secondary outcomes (Barnes Akathisia Rating Scale [BARS], Simpson-Angus Scale [SAS], HAM-A, Anger Attacks Questionnaire, Arizona Sexual Experience Scale [ASEX], CGI-I, CGI-S, and CGI-Efficacy Index).

McIntyre and colleagues[3] conducted a double-blind, randomized, placebo-controlled study to evaluate the use of quetiapine as an adjunct to SSRIs or SNRIs for major depression (*DSM-IV*) with residual depressive and prominent anxiety symptoms. Fifty-eight patients, following at least 6 weeks of SSRI/SNRI treatment, were randomized to receive quetiapine (n=29) or placebo (n=29) for 8 weeks. Quetiapine was given as a single daily dose at night, and was initiated at 50 mg/day for 7 days and titrated to 100 mg/day for 7 days, 200 mg/day for 7 days, and then to a maximum of 600 mg/day thereafter. The primary outcome was the mean change from baseline to week 8 (last observation carried forward [LOCF]) in the HAM-D and the HAM-A. Response was defined as a ≥50% reduction in HAM-D or HAM-A total scores from baseline to week 8. Remission was defined as a HAM-D or HAM-A total score of 7 or lower at week 8.

The mean quetiapine dose was 182 mg/day. Eighteen quetiapine-treated (mean dose 202 mg/day) and 16 placebo-treated patients completed the study. Significant improvements from baseline were seen in HAM-D at week 1 (-6.5 vs. -2.9; p≤0.01) and at week 8 (-11.2 vs. -5.5; p≤0.01) and in the HAM-A at week 1 (-7.4 vs. -3.4; p≤0.01) and at week 8 (-12.5 vs. -5.9; p≤0.01), in the quetiapine vs. placebo groups, respectively. HAM-D response rates (48% vs. 28%) and remission rates (31% vs. 17%) were higher in the quetiapine vs. placebo groups, respectively. HAM-A response rates (62% vs. 28%) and remission rates (41% vs. 17%) were also higher in the quetiapine vs. placebo groups, respectively. Most common reasons for study withdrawal included adverse events in the quetiapine group (n=8) and inefficacy in the placebo group (n=9). Most common adverse events reported included sedation/somnolence/lethargy (n=25 vs. n=14), dry mouth (n=13 vs. n=4), and increased weight (n=10 vs. n=3) in the quetiapine vs. placebo groups respectively. The mean change in body weight was +2.36 kg in the quetiapine group and -0.29 in the placebo group.

Mattingly and colleagues[4] conducted an 8-week, double-blind, randomized, placebo-controlled trial, in order to investigate the adjunct use of quetiapine in patients with a primary diagnosis of major depression and partially responsive to at least 6 weeks of SSRI/SNRI treatment. Patients with baseline HAM-D-17 scores ≥20 were randomized to receive quetiapine 200-400 mg/day (mean dose 268 mg/day) (n=23) or placebo (n=13) in addition to SSRI/SNRI treatment. The primary outcome measure was HAM-D-17 scores at week 8. HAM-D-17 scores significantly improved from baseline (25.0 vs. 24.5) to endpoint (8.3 vs. 14.7) in the quetiapine vs. placebo groups, respectively (p<0.01). MADRS scores significantly improved from baseline (32.4 vs. 33.5) to endpoint (15.4 vs. 24.8) in the quetiapine vs. placebo groups, respectively (p<0.05). More patients in the quetiapine group responded to treatment (≥50% reduction in HAM-D-17 score) vs. placebo (67% vs. 27%, p=0.015), and achieved remission (HAM-D-17 score <7) (43% vs. 15%, p<0.05). Patients receiving quetiapine also had significantly lower CGI-S and CGI-I scores at endpoint vs. placebo. Common adverse events for quetiapine vs. placebo included headache (29.2% vs. 45.4%), fatigue (29.2% vs. 18.2%), dry mouth (12.5% vs. 0%), and sedation/somnolence (8.3% vs. 9.1%).

Yargic and colleagues[5] evaluated the effectiveness of adding quetiapine to existent paroxetine therapy for the treatment of anxiety associated with depression in an 8-week prospective, single-blind, controlled trial. Enrolled patients (n=112), randomized to receive paroxetine only or paroxetine + quetiapine, had a diagnosis of major depression (*DSM-IV*), a score of ≥2 on items 10 and 11 (associated with anxiety) from the HAM-D scale, and a score of ≥26 on the HAM-A scale. The primary efficacy endpoint was the comparison between the 2 groups in changes in the HAM-A scale. Evaluations were made at baseline, and weeks 1, 2, 4, 6, and 8. Statistical significance was assigned to p-values <0.008 for the study parameters HAM-A, HAM-D, and CGI scales. A p-value <0.05 was considered statistically significant for all other variables.

Mean daily paroxetine doses were not significantly different between the 2 groups throughout the study. HAM-A scores were similar for the paroxetine only and paroxetine + quetiapine groups at baseline and did not differ significantly at any time-point in the study. However, the absolute decrease in HAM-A score was significantly greater in the paroxetine + quetiapine for weeks 2, 4, 6, and the LOCF (p= 0.005, 0.005, 0.002, 0.003, respectively) when compared to the paroxetine only group. The HAM-D score was significantly higher for the paroxetine + quetiapine group compared to the paroxetine only group (p=0.001) at baseline. However, due to a faster decrease in HAM-D scores in the combination group, the difference between the mean HAM-D scores of groups became statistically non-significant, beginning at week 1. The paroxetine + quetiapine group score for HAM-D continued to decrease more rapidly than the paroxetine only group and was significantly different for weeks 2, 4, 6, and LOCF (p=0.001, <0.001, =0.003, <0.001, respectively). The absolute decrease in HAM-D score was significantly greater for the paroxetine + quetiapine group compared to paroxetine only group during the whole study period. The mean CGI-I score was significantly greater in the paroxetine + quetiapine group at week 4 but was not significantly different at any other time. A total of 28 patients withdrew from the study. Two patients in the paroxetine only group, and 9 patients in the paroxetine + quetiapine group withdrew due to adverse events. To differentiate ongoing depression and anxiety from treatment adverse events, emerging complaints or symptoms were counted as adverse events. Insomnia was significantly more frequent in the paroxetine only group from weeks 2 to 6 compared to the paroxetine + quetiapine group. At week 4, 13.3% of the paroxetine only group reported an "increase in anxiety" which differed significantly from the 2.0 % reported in the paroxetine + quetiapine group. "Increased appetite" was reported in 20.4% of the paroxetine + quetiapine group at week 6 which differed significantly from the 2.4% reported in the paroxetine only group. No other significant between-group differences were reported in the frequency of other adverse events, including percent increase in body weight.

Hussain and colleagues[6] conducted a randomized study in 72 patients diagnosed with MDD (*DSM-IV-TR*) to compare the efficacy of monotherapy treatment with an SSRI to adjunct quetiapine therapy in the treatment of MDD and in the maintenance of symptom remission. Patients were randomly assigned to one of 4 treatment groups: paroxetine monotherapy; venlafaxine monotherapy; paroxetine and quetiapine combination therapy; and venlafaxine and quetiapine combination therapy. HAM-D-17 was assessed at baseline, and at weeks 1, 3, 6, and 12, and every 6 months for 3 years thereafter. Categorical HAM-D scores improved from baseline to week 1 in the combination therapy groups. Improvement in and maintenance of HAM-D scores in all 4 groups were seen at week 3 and were maintained at assessments over the 3 years of the study. Significant improvement in depressive symptoms and the development of

remission occurred more frequently in the paroxetine and quetiapine combination group. Eighteen patients withdrew from the study. A greater overall frequency of adverse events was seen in the combination therapy groups vs. the monotherapy groups. The number of hospitalization days for the treatment of depressive symptoms was greater in the monotherapy groups (11.9 days) vs. the combination therapy groups (7.1 days).

Khullar and colleagues[7] conducted an 8-week randomized study in 16 patients with a current *DSM-IV* major depressive episode without psychotic features who had residual symptoms after at least 6 weeks of treatment with an adequate dose of a SSRI/SNRI. Patients were randomized to receive either placebo or flexibly dosed adjunctive quetiapine (100-600 mg once daily; mean dose 350 mg). One patient withdrew from the study because the patient discontinued venlafaxine prior to receiving treatment. Using the LOCF analysis, significantly greater mean changes were observed in the HAM-D-17 (11.87 vs. 4.86; p=0.018), MADRS (14.88 vs. 5.29; p=0.007), and HAM-A (11 vs. 4.14; p=0.007) for the quetiapine (n=8) vs. placebo (n=7) groups, respectively. Three out of 8 patients in the quetiapine group met remission criteria (HAM-D-17 <7) vs. none in the placebo group. No significant differences were seen between the 2 groups in the Pittsburgh Sleep Quality Index (PSQI), Sheehan Disability Scale (SDS), CGI-S, CGI-I, weight gain, and measures of cholesterol/glucose.

Open-Label Studies

Targum and colleagues[8] conducted a 4-week open-label study to evaluate the anxiolytic, antidepressive, and sleep efficacy and safety quetiapine when added to an existing SSRI treatment regimen in adult patients with MDD who presented with persistent anxiety. Enrolled patients (n=22) met *DSM-IV* criteria for MDD, were taking stable doses of an SSRI or venlafaxine for at least 6 weeks prior to baseline, and had a HAM-A score ≥20 and a HAM-D score ≤17 at screening and baseline. Quetiapine was initiated at 25 mg on day 1, and flexibly dosed BID based on clinical response thereafter, while the antidepressant dose remained unchanged. Antidepressant therapy included venlafaxine (n=5), citalopram (n=7), paroxetine (n=3), sertraline (n=4), and fluoxetine (n=3). Stable quetiapine doses were achieved between weeks 1 and 2, with a mean dose of 105.9 mg/day (range, 25-300 mg/day). The mean HAM-A score improved significantly from 25.6 at baseline to 9.2 at endpoint (p<0.001). HAM-D improved from 15.0 at baseline to 7.2 at endpoint (p<0.001), with observed changes primarily in the anxiety, somatic, and sleep items. Nine patients described sedative-like effects that were mostly transient within the first week of treatment. Five patients withdrew within the first week. Of the 17 patients who completed the study, 13 had a >50% decrease from baseline in HAM-A scores.

Sagud and colleagues[9] conducted a prospective, open-label, non-comparative study of 18 patients with *DSM-IV* MDD, who have failed at least 2 antidepressant trials of different classes. Average duration of depressive episode was 11.2 months, and 3.77 antidepressants have been given to treat the current episode. Quetiapine was added to the patient's current antidepressive treatment according to usual dose-titration recommendation. Depressive symptoms were rated by HAM-D-17 scale at baseline, weekly during the first 8 weeks of treatment, and monthly thereafter. Fourteen out of 18 patients responded (≥50% reduction of baseline HAM-D-17 score) to adjunctive quetiapine treatment. Three patients were non-responders, and 1 patient was

withdrawn due to hypotension. Mean time of response to quetiapine was 3.65 weeks and mean quetiapine dose was 325.4 mg/day. All responders continued taking quetiapine, and mean duration of quetiapine maintenance treatment was 6.15 months at time of the abstract submission.

Enclosure(s):

- SEROQUEL Prescribing Information.

Reference(s):

[1] SEROQUEL Prescribing Information.
[2] Martinez J, Garakani A, Marcus S, et al. A randomized, double-blind, placebo-controlled trial of quetiapine combined with fluoxetine in major depressive disorder [poster]. Presented at: the 59th Institute of Psychiatric Services Conference; October 11-14, 2007; New Orleans, LA.
[3] McIntyre A, Gendron A, McIntyre A. Quetiapine augmentation of SSRIs/SNRIs in major depression with anxiety [poster]. Presented at: the 159th Annual Meeting of the American Psychiatric Association; May 20-25, 2006; Toronto, Canada.
[4] Mattingly G, Ilivicky H, Canale J, et al. Quetiapine augmentation for treatment-resistant depression [poster]. Presented at: the 159th Annual Meeting of the American Psychiatric Association; May 20-25, 2006; Toronto, Canada.
[5] Yargic LI, Corapcioglu A, Kocabasoglu N, et al. A prospective randomized single-blind, multicenter trial comparing the efficacy and safety of paroxetine with and without quetiapine therapy in depression associated with anxiety. *Int J Psychiatry Clin Pract.* 2004;8(4):205-211.
[6] Hussain MZ, Waheed W, Hussain S, et al. A comparison of unipolar depression treatment using antidepressants alone versus using antidepressants in combination with quetiapine [abstract]. *Eur Neuropsychopharmacol.* 2005;15(suppl 3):S453-S454. Abstract P2 143.
[7] Khullar A, Chokka P, Fullerton D, et al. Quetiapine as treatment of non-psychotic unipolar depression with residual symptoms: double blind, randomized, placebo controlled study [poster]. Presented at: the 159th Annual Meeting of the American Psychiatric Association; May 20-25, 2006; Toronto, Canada.
[8] Targum S, Hassman H, Bastani B, et al. Use of quetiapine in treating nonpsychotic anxiety and depressive disorder. *Schizophr Bull.* 2005;31(2):504-505.
[9] Sagud M, Mihaljevic Peles A, Mueck Seler D, et al. Quetiapine augmentation in treatment-resistant depression [abstract]. *Eur Neuropsychopharmacol.* 2005;15(suppl 3):S444. Abstract P2 120.

SEROQUEL XR-Use for Major Depressive Disorder (MDD)

Prescribing Information[1]

SEROQUEL XR is a psychotropic agent belonging to the dibenzothiazepine chemical class.

Indications

SEROQUEL XR is indicated for the acute and maintenance treatment of schizophrenia.

Boxed Warning

***Suicidality and Antidepressant Drugs* - Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL XR is not approved for use in pediatric patients. SEROQUEL XR is not approved for use in the treatment of depression, however, an immediate release form of quetiapine (SEROQUEL) is approved for the treatment of bipolar depression. (See Warnings and Precautions: Clinical Worsening and Suicide Risk).**

SEROQUEL XR is not indicated for the treatment of major depressive disorder (MDD). Please refer to the SEROQUEL XR Prescribing Information for complete product information.

Clinical Data

Quetiapine Monotherapy

Cutler and colleagues[2] evaluated the efficacy and tolerability of once daily quetiapine extended-release (XR) monotherapy vs. placebo in 612 patients with major depressive disorder (MDD). Patients (18-65 years of age) with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* diagnosis of MDD (single episode or recurrent), Hamilton Rating Scale for Depression (HAM-D) ≥22, and HAM-D Item 1 (depressed mood) score ≥2 at enrollment and randomization were enrolled. This multicenter, double-blind, parallel-group, 8-week study was comprised of a 6-week active treatment/randomized phase in which patients received fixed doses of quetiapine XR 150 mg/day (Days 1-2, 50 mg/day; Days 3-42, 150 mg/day), or quetiapine XR 300 mg/day (Days 1-2, 50 mg/day; Days 3-4, 150 mg/day; Days 5-42, 300 mg/day), duloxetine 60 mg/day (as an active control arm), or placebo, followed

by a 2-week post-treatment drug discontinuation phase. The modified intent-to-treat (MITT) population was comprised of 587 patients. Mean age ranged from 40.2 to 42.3 years, and the majority of patients were female (range 51.0% to 64.5%). Results for the primary efficacy endpoint (change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale [MADRS]) total score are shown in Table I.

Table I: Change in MADRS Total Score From Randomization Over Time (LOCF;MITT Population).
Adapted from the poster presented at the 46th Annual Meeting of the American College of Neuropsychopharmacology; December 9-13, 2007; Boca Raton, FL, USA.

Timepoint	Quetiapine XR 150 mg/day n=147	Quetiapine XR 300 mg/day n=147	Duloxetine n=141	Placebo n=152
Baseline	29.8	30.1	30.4	30.3
Week 1 (Day 8)	-8.36*	-8.19*	-6.81†	-6.01
Week 6	-14.81‡	-15.29‡	-14.64*	-11.18

LOCF=last observation carried forward; MADRS=Montgomery-Asberg Depression Rating Scale; MITT=modified intent-to-treat; XR=extended-release.
*p<0.01 vs. placebo
†p=0.3 vs. placebo
‡p<0.001 vs. placebo

For the secondary efficacy variables, at Week 6, response rates (≥ 50% reduction in MADRS total score from baseline to Week 6) were significantly higher with quetiapine XR 150 mg/day (54.4%), quetiapine XR 300 mg/day (55.1%), and duloxetine (49.6%) compared with placebo (36.2%) ($p<0.01$, $p<0.01$, $p<0.05$, respectively). Remission rates (MADRS total score ≤8 at Week 6) were significantly higher than placebo (20.4%) for quetiapine XR 300 mg/day (32.0%) and duloxetine (31.9%) ($p<0.05$ for both), but the difference between quetiapine XR 150 mg/day (26.5%) and placebo was not significant. HAM-D and Hamilton Rating Scale for Anxiety (HAM-A) total scores were significantly reduced from baseline to Week 6 in all active treatment groups compared with placebo. Quetiapine XR 150 mg/day, 300 mg/day, and duloxetine all significantly improved the Clinical Global Impression-Severity of Illness (CGI-S) mean scores from baseline. A significantly greater proportion of patients had CGI-Improvement (CGI-I) score of 1 ("very much" improved) or 2 ("much" improved) at Week 6 in the active treatment groups compared with placebo.

The safety population was comprised of 610 patients. The incidences of serious adverse events (AEs) were low in all active treatment groups (≤2%); no serious AEs were reported in the placebo group. During the randomized treatment phase, the percentage of patients who discontinued due to AEs was 21.0%, 15.1%, 17.4%, and 5.7% in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine, and placebo groups, respectively. The most common reasons for discontinuation in either quetiapine XR group were somnolence or sedation. Common AEs reported by ≥5% of quetiapine-treated patients included dry mouth, sedation, somnolence, dizziness, headache, constipation, irritability, dyspepsia, fatigue, nausea, vision blurred, increased appetite, and abnormal dreams. AEs potentially related to sexual dysfunction or extrapyramidal symptoms (EPS) occurred more frequently with duloxetine than with quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo.

Mean changes from baseline in glucose (mg/dL) were +3.29, +3.87, +2.31, and +1.61 in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine, and placebo groups, respectively. The numbers of patients with a clinically important elevated glucose value

(≥126 mg/dL) during an assumed fasting status were quetiapine XR 150 mg/day (n=3), quetiapine XR 300 mg/day (n=6), duloxetine (n=1), and placebo (n=1). Mean changes from baseline in total cholesterol, low density lipoprotein (LDL), and high density lipoprotein (HDL) decreased in all treatment groups. For triglycerides (mg/dL), the mean changes from baseline were +17.9, +16.0, +5.1, and -2.5 in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine, and placebo groups, respectively. Mean changes from baseline in weight (kg) were +1.0, +1.3, -0.5, and +0.1 in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine, and placebo groups, respectively.

Quetiapine Adjunct Therapy to Antidepressants

Earley and colleagues[3] conducted a multicenter, double-blind, parallel-group, placebo controlled, double-dummy, 6-week study to evaluate the efficacy and tolerability of quetiapine XR as an adjunct to antidepressant therapy in 493 patients with MDD who had shown an inadequate response to their current antidepressant treatment. The study was conducted in Australia, Europe, North America, and South Africa. Outpatients (18-65 years of age) with a *DSM-IV-TR* diagnosis of MDD (single episode or recurrent) and a history of an inadequate response during the current episode to at least one antidepressant treatment given for ≥6 weeks at adequate doses, HAM-D ≥20, and HAM-D Item 1 (depressed mood) score ≥2 at enrollment and randomization, were enrolled were enrolled. Following a 2-week washout period (of all medications other than current antidepressant), eligible patients were randomized to receive quetiapine XR 150 mg/day (Days 1-2, 50 mg/day; Days 3 onward, 150 mg/day), or quetiapine XR 300 mg/day (Days 1-2, 50 mg/day; Days 3-4, 150 mg/day; Days 5 onward, 300 mg/day), or placebo, plus antidepressant treatment that was ongoing ≥6 weeks before entering the study and maintained at the same dose throughout the study. Antidepressants on entry were amitriptyline, escitalopram, citalopram, duloxetine, fluoxetine, bupropion, venlafaxine, paroxetine, and sertraline. The MITT population, defined as all randomized patients who received assigned study medication and had both a randomization and at least one post-randomization MADRS score, was comprised of 487 patients. Mean age ranged from 44.8 to 46.0 years, and the majority of patients were female (range 65.0% to 69.3%). In addition, treatment groups were well matched in terms of the antidepressants used as combination therapy. Results for the primary efficacy endpoint (change from baseline to Week 6 in MADRS total score) are shown in Table II.

Table II: Change in MADRS total score from randomization over time (LOCF; MITT population). Adapted from the poster presented at the 46th Annual Meeting of the American College of Neuropsychopharmacology; December 9-13, 2007; Boca Raton, FL, USA.

Time point	Quetiapine XR 150 mg/day n=160	Quetiapine XR 300 mg/day n=161	Placebo n=160
Baseline	28.6	28.4	28.2
Week 1	-6.52*	-6.38*	-4.16
Week 6	-15.26†	-14.94†	-12.21

LOCF=last observation carried forward; MADRS=Montgomery-Asberg Depression Rating Scale; MITT=modified intent-to-treat; XR=extended-release
*p<0.001 vs. placebo
†p<0.01 vs. placebo

For the secondary efficacy variables, response rates (≥ 50% reduction in MADRS total score from baseline to Week 6) were significantly higher for quetiapine XR 300 mg/day (57.8%) than placebo (46.3%, p<0.05). For quetiapine XR 150 mg/day, the response rate at Week 6 (55.4%)

was numerically but not significantly higher than placebo (p=0.107). Remission rates (MADRS total score ≤8 at Week 6) were significantly higher for quetiapine XR 150 mg/day (36.1%) than placebo (23.8% p<0.05), but not significant in the quetiapine XR 300 mg/day group (31.1%, p=0.126). HAM-D and HAM-A total scores were significantly reduced from baseline to Week 6 in both the quetiapine XR 150 mg/day and 300 mg/day treatment groups compared with placebo. Quetiapine XR 150 mg/day and 300 mg/day both significantly improved CGI-S mean scores from baseline. A greater proportion of patients in the quetiapine XR 150 mg/day and 300 mg/day groups had a CGI-I score of 1 or 2 at Week 6 compared with placebo; the difference vs. placebo was significant for quetiapine XR 150 mg/day and approached statistical significance for quetiapine XR 300 mg/day.

The safety population was comprised of 491 patients. The incidence of serious AEs was low (≤2%) in the 3 treatment groups. During the randomized treatment phase, the percentage of patients who discontinued due to AEs was 6.6%, 11.7%, and 3.7% in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively. The most common reasons for discontinuation in either quetiapine XR group were somnolence, sedation, or fatigue. Common AEs reported by ≥5% of quetiapine-treated patients included dry mouth, somnolence, fatigue, sedation, constipation dizziness, headache, and nausea.

Mean changes from baseline in glucose (mg/dL) were -0.19, +2.05, and +1.89 in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively. The numbers of patients with a clinically important elevated glucose value (≥126 mg/dL) during an assumed fasting status were quetiapine XR 150 mg/day (n=5), quetiapine XR 300 mg/day (n=9), and placebo (n=5). Mean changes from baseline in HDL decreased in all treatment groups. Total cholesterol and LDL increased in quetiapine-treated patients compared with decreases in the in placebo group. For triglycerides (mg/dL), the mean changes from baseline were +15.4, +14.2, and -6.0 in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively. Mean changes from baseline in weight (kg) were +0.9, +1.0, and 0.0 in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively.

Enclosure(s):

- SEROQUEL XR Prescribing Information.

Reference(s):

[1] SEROQUEL XR Prescribing Information.
[2] Cutler A, Montgomery S, Feifel D, et al. Extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with major depressive disorder (MDD): results from a double-blind randomized phase III Study [poster]. Presented at: the 46th American College of Neuropsychopharmacology Annual Meeting; December 9-13, 2007; Boca Raton, FL, USA.
[3] Earley W, McIntyre A, Bauer M, et al. Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) as add-on to antidepressants in patients with major depressive disorder (MDD): results from a double-blind, randomized, phase III study [poster]. Presented at the 46th American College of Neuropsychopharmacology Annual Meeting; December 9-13, 2007; Boca Raton, FL, USA.

Rev: 10/07 SIC 30417-03

SEROQUEL

(quetiapine fumarate)

TABLETS

RX ONLY

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. Analyses of seventeen placebo-controlled trials (modal 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 appeared 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.

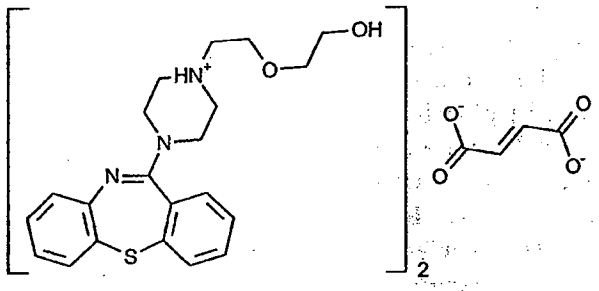
Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in pediatric patients. (See Warnings:

Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

DESCRIPTION

SEROQUEL® (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo *[b,f]* [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (round, peach), 50 mg (round, white), 100 mg (round, yellow), 200 mg (round, white), 300 mg (capsule-shaped, white), and 400 mg (capsule-shaped, yellow) tablets.
Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg and 400 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and

adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other drugs having efficacy in the treatment of schizophrenia and bipolar disorder, is unknown. However, it has been proposed that the efficacy of SEROQUEL in schizophrenia and its mood stabilizing properties in bipolar depression and mania are mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL.
SEROQUEL's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn,

neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups:

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION).**

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed

typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole (See Drug Interactions under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (See **Drug Interactions** under **PRECAUTIONS**).

Clinical Efficacy Data

Bipolar Disorder

Depression

The efficacy of SEROQUEL for the treatment of depressive episodes associated with bipolar disorder was established in 2 identical 8-week, randomized, double-blind, placebo-controlled studies (N=1045). These studies included patients with either bipolar I or II disorder and those with or without a rapid cycling course. Patients randomized to SEROQUEL were administered fixed doses of either 300 mg or 600 mg once daily.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10 item clinician-rated scale with scores ranging from 0 to 60. The primary endpoint in both studies was the change from baseline in MADRS score at week 8. In both studies, SEROQUEL was superior to placebo in reduction of MADRS score. Improvement in symptoms, as measured by change in MADRS score relative

to placebo, was seen in both studies at Day 8 (week 1) and onwards. In these studies, no additional benefit was seen with the 600 mg dose. For the 300 mg dose group, statistically significant improvements over placebo were seen in overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q(SF).

Mania

The efficacy of SEROQUEL in the treatment of acute manic episodes was established in 3 placebo-controlled trials in patients who met DSM-IV criteria for Bipolar I disorder with manic episodes. These trials included patients with or without psychotic features and excluded patients with rapid cycling and mixed episodes. Of these trials, 2 were monotherapy (12 weeks) and 1 was adjunct therapy (3 weeks) to either lithium or divalproex. Key outcomes in these trials were change from baseline in the Young Mania Rating Scale (YMRS) score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of SEROQUEL with lithium or divalproex.

The primary rating instrument used for assessing manic symptoms in these trials was YMRS, an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score).

The results of the trials follow:

Monotherapy

In two 12-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking SEROQUEL were dosed in a range between 400 and 800 mg per day.

Adjunct Therapy

In this 3-week placebo-controlled trial, 170 patients with acute bipolar mania (YMRS $\geq$ 20) were randomized to receive SEROQUEL or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an

adequate treatment course of lithium or divalproex prior to randomization. SEROQUEL was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score.

The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 and 800 mg per day. In a similarly designed trial (n=200), SEROQUEL was associated with an improvement in YMRS scores but did not demonstrate superiority to placebo, possibly due to a higher placebo effect.

Schizophrenia

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (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.

The results of the trials follow:

1. In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the

BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 mg/day were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

2. In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

3. In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

Bipolar Disorder

SEROQUEL is indicated for the treatment of both:

- depressive episodes associated with bipolar disorder
- acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex.

Depression

The efficacy of SEROQUEL was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or II patients (See **CLINICAL PHARMACOLOGY**). Effectiveness has not

been systematically evaluated in clinical trials for more than 8 weeks.

Mania

The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania (See **CLINICAL PHARMACOLOGY**). Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy.

The physician who elects to use SEROQUEL for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

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 (See **CLINICAL PHARMACOLOGY**).

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 (See **DOSAGE AND ADMINISTRATION**).

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).

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in

	Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are

experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. 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.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SEROQUEL is approved for use in treating adult bipolar depression.

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 hyperpyrexia, 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 (e.g., 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 reintroduction of drug therapy 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, dyskinetic 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 the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given 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 dose 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 ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel (see **ADVERSE REACTIONS, Hyperglycemia**). 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 anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General:

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) 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 patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

Leukopenia, Neutropenia and Agranulocytosis: In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related

to atypical antipsychotic agents, including SEROQUEL. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. 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.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $<1000/mm^3$) should discontinue SEROQUEL and have their WBC followed until recovery (See ADVERSE REACTIONS).

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 lenticular changes 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 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) 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, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: 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 TBG 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 0.7% (26/3489) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproate, 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 levels, 3 had simultaneous low free T4 levels.

Cholesterol and Triglyceride Elevations: In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥240 mg/dL and triglycerides ≥200 mg/dL were 16% and 23% for SEROQUEL treated patients respectively compared to 7% and 16% for placebo patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for SEROQUEL treated patients respectively, compared to 6% and 9% for placebo patients respectively.

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. In bipolar depression trials, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in two 8-week placebo-controlled trials was 1% for SEROQUEL and 2% for placebo.

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-titration. In schizophrenia trials, somnolence was reported in 18% 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 adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. In bipolar depression trials, somnolence was reported in 28% of patients on SEROQUEL compared to 7% of placebo patients. 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 (see Renal Impairment and

Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) 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**).

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.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for SEROQUEL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SEROQUEL.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families

and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

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 advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity 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.

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 appropriate care in avoiding overheating and dehydration.

Leukopenia/Neutropenia:

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL.

Laboratory Tests

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 PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis)**

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 certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

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 (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**).

Divalproex: Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum

plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance.

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 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: 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 335% increase in maximum plasma concentration of quetiapine. Caution (reduced dosage) is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, erythromycin, and protease inhibitors).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Divalproex: The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant.

Lithium: Concomitant administration 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 (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (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/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 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/m^2 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 subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell 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-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- 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 considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General).**

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* 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 oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate 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/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 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/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C:

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed 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/m^2 basis or in rabbits at 25

to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal 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/m^2 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 treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established. Anyone considering the use of SEROQUEL in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use: Of the approximately 3700 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 orthostasis, 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 (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for SEROQUEL consisting of over 3700 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) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia.

Of these approximately 3700 subjects, approximately 3400 (2300 in schizophrenia, 405 in acute bipolar mania, and 698 in bipolar depression) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 992.6 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 events 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 events without first grouping similar types of events into a smaller number of standardized event categories.

In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events

for schizophrenia and bipolar mania. MedDRA terminology has been used to classify reported adverse events for bipolar depression.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo- Controlled Trials

Bipolar Disorder:

Depression: Overall, discontinuations due to adverse events 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 events 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 events (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 **PRECAUTIONS**):

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

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 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 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.

Table 2. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)

Body System/ Preferred Term	SEROQUEL (n=719)	PLACEBO (n=404)
Body as a Whole		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal Pain	4%	1%
Back Pain	3%	1%
Fever	2%	1%
Cardiovascular		
Tachycardia	6%	4%
Postural Hypotension	4%	1%
Digestive		
Dry Mouth	9%	3%
Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%

Gastroenteritis	2%	0%
Gamma Glutamyl Transpeptidase Increased	1%	0%
Metabolic and Nutritional		
Weight Gain	5%	1%
SGPT Increased	5%	1%
SGOT Increased	3%	1%
Nervous		
Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%
Respiratory		
Pharyngitis	4%	3%
Rhinitis	3%	1%
Skin and Appendages		
Rash	4%	2%
Special Senses		
Amblyopia	2%	1%

[1] Events 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 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%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%).

Table 3 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 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 Experience Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)

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

[1] Events 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.

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%).

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events 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.

Table 4. Treatment-Emergent Adverse Experience Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression

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

Disorders		
Nasal Congestion	5%	3%

[1] Events 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 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 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 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-relatedness of 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 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.

SEROQUEL

Dose Groups	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 events 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 events (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 **PRECAUTIONS**).

Weight Gain: In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥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 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 (see **PRECAUTIONS**).

In placebo controlled monotherapy clinical trials involving 3368 patients on SEROQUEL and 1515 on placebo, the incidence of at least one occurrence of neutrophil count <1.0 x 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 SEROQUEL, compared to 0.1% (2/1349) in patients treated with placebo. **(See PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis)**

In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed.

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 (≥ 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 ≥126 mg/dl or a non fasting blood glucose ≥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 ≥200 mg/dl was 1.7% and the incidence of a

fasting treatment-emergent blood glucose level ≥ 126mg/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 **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART 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 2 or elsewhere in labeling, those events for which a drug cause was remote, 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: ***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: ***Infrequent:*** 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: ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: ***Infrequent:*** 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: ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.
*adjusted for gender

Post Marketing Experience:
Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: anaphylactic reaction, and restless legs..
Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy, hyponatremia, myocarditis, rhabdomyolysis, syndrome of inappropriate antidiuretic

hormone secretion (SIADH), and Stevens-Johnson Syndrome (SJS).

DRUG ABUSE AND DEPENDENCE

Controlled 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 any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, 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.

OVERDOSAGE

Human experience: In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (**See PRECAUTIONS: Orthostatic Hypotension**) One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation.

Management of Overdosage:

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative

should be considered. The possibility of obtundation, seizure or dystonic reaction 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 antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage 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 instituted. 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 cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Bipolar Disorder

Depression

Usual Dose: SEROQUEL should be administered once daily at bedtime to reach 300 mg/day by day 4.

Recommended Dosing Schedule

Day	Day 1	Day 2	Day 3	Day 4
SEROQUEL	50 mg	100 mg	200 mg	300 mg

In the clinical trials supporting effectiveness, the dosing schedule was 50 mg, 100 mg, 200 mg and 300 mg/day for days 1-4 respectively. Patients receiving 600 mg increased to 400 mg on day 5 and 600 mg on day 8 (Week 1). Antidepressant efficacy was demonstrated with SEROQUEL at both 300 mg and 600 mg however, no additional benefit was seen in the 600 mg group.

Mania

Usual Dose: When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in bid doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in bid divided doses. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicates that the majority of patients responded between 400 to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Schizophrenia

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 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 adjustments, if indicated, should generally occur at intervals 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.

Efficacy in schizophrenia 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 300mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of

25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered 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 the patient treated with SEROQUEL should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Antipsychotics: There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to SEROQUEL, or concerning concomitant administration with antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one

side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

50 mg Tablets (NDC 0310-0278) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '50' on one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' 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 'SEROQUEL' 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.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets, and hospital unit dose packages of 100 tablets.

400 mg Tablets (NDC 0310-0279) yellow, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '400' 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 15-30°C (59-86°F) [See USP].

ANIMAL TOXICOLOGY

Quetiapine caused 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; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 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 effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 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 cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

• Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
• Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
• Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:
• thoughts about suicide or dying
• attempts to commit suicide
• new or worse depression
• new or worse anxiety
• feeling very agitated or restless
• panic attacks
• trouble sleeping (insomnia)
• new or worse irritability
• acting aggressive, being angry, or violent
• acting on dangerous impulses
• an extreme increase in activity and talking (mania)
• other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?
• **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.

• **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it.
Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

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

SEROQUEL is a trademark of the AstraZeneca group of companies

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Made in USA
Rev. 10/07 SIC 30417-03

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SEROQUEL XR safely and effectively. See full prescribing information for SEROQUEL XR.

SEROQUEL XR *(quetiapine fumarate) Extended-Release Tablets*

Initial U.S. Approval: 1997

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA ***See full prescribing information for complete boxed warning.***

- **Atypical antipsychotic drugs are associated with an increased risk of death (5.1)**
- **Quetiapine is not approved for elderly patients with Dementia-Related Psychoses (5.1)**

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS ***See full prescribing information for complete boxed warning.***

- **Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders (5.2)**
- **SEROQUEL XR is not approved for the treatment of depression, however, an immediate release form of quetiapine (Seroquel) is approved for the treatment of bipolar depression. (5.2)**

----------RECENT MAJOR CHANGES----------

WARNING: Suicidality and Antidepressant Drugs *(see Boxed Warning)* 06/2007
Warnings and Precautions, Suicidality and Antidepressant Drugs (5.2) 06/2007
Warning: Hyperglycemia and Diabetes Mellitus (5.3), 06/2007
Warnings and Precautions, Leukopenia, Neutropenia, and Agranulocytosis (5. 6) 11/2007

----------INDICATIONS AND USAGE----------

SEROQUEL XR is an atypical antipsychotic agent indicated for:

- The acute and maintenance treatment of schizophrenia (1)

----------DOSAGE AND ADMINISTRATION----------

Schizophrenia: SEROQUEL XR should be administered once daily, preferably in the evening. The recommended initial dose is 300 mg. The effective dose range for SEROQUEL XR is 400 – 800 mg per day depending on the response and tolerance of the individual patient. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day. Individual dosage adjustments may be necessary. SEROQUEL XR Tablets should be swallowed whole and not split, chewed or crushed. SEROQUEL XR should be taken without food or with a light meal. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-Release Tablets: 200 mg, 300 mg, and 400 mg

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

- **Increased Mortality in Elderly Patients with Dementia Related Psychoses:** Atypical antipsychotic drugs, including quetiapine, are associated with an increased risk of death; causes of death are variable. (5.1)
- **Suicidality and Antidepressant Drugs:** Seroquel XR is not approved for the treatment of depression, however, an immediate release form of quetiapine (Seroquel) is approved for the treatment of bipolar depression. (5.2)
- **Hyperglycemia and Diabetes Mellitus (DM):** Ketoacidosis, hyperosmolar coma and death have been reported in patients treated with atypical antipsychotics, including quetiapine. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. When starting treatment, patients with DM risk factors should undergo blood glucose testing before and during treatment. (5. 3)
- **Neuroleptic Malignant Syndrome (NMS):** Potentially fatal symptom complex has been reported with antipsychotic drugs, including quetiapine. (5. 4)
- **Orthostatic Hypotension:** Associated dizziness, tachycardia and syncope especially during the initial dose titration period. (5. 5)
- **Leukopenia, Neutropenia and Agranulocytosis:** have been reported with atypical antipsychotics including SEROQUEL XR. Patients with a pre-existing low white cell count (WBC) or a history of leukopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months of treatment and should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors. (5. 6)
- **Tardive Dyskinesia** may develop acutely or chronically. (5. 7)
- **Cataracts:** Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination should be done when starting treatment and at 6 months intervals during chronic treatment. (5. 8)
- **Hyperlipidemia** (5. 11)
- The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. (5.18)
- See Full Prescribing Information for additional **WARNINGS and PRECAUTIONS.**

---------- ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥5% and greater than placebo) are dry mouth, constipation, dyspepsia, sedation, somnolence, dizziness, and orthostatic hypotension. (6.1) **To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

----------DRUG INTERACTIONS----------

- **P450 3A Inhibitors:** May decrease the clearance of quetiapine. Lower doses of quetiapine may be required. (7.1)
- **Hepatic Enzyme Inducers:** May increase the clearance of quetiapine. Higher doses of quetiapine may be required with phenytoin or other inducers. (7.1)
- **Centrally Acting Drugs:** Caution should be used when quetiapine is used in combination with other CNS acting drugs. (7)
- **Antihypertensive Agents:** Quetiapine may add to the hypotensive effects of these agents. (7)
- **Levodopa and Dopamine Agents:** Quetiapine may antagonize the effect of these drugs. (7)

----------USE IN SPECIFIC POPULATIONS----------

- **Geriatric Use:** For the initial dosing in the elderly use the immediate release formulation of SEROQUEL instead of SEROQUEL XR. Consider a lower starting dose (25 mg/day immediate release formulation), slower titration, and careful monitoring during the initial dosing period in the elderly. (2.2, 8.5)
- **Hepatic Impairment:** For the initial dosing in patients with hepatic impairment, use the immediate release formulation of SEROQUEL instead of SEROQUEL XR. Lower starting doses (25 mg/day immediate release formulation) and slower titration may be needed. (2.2, 8.7, 12.3)
- **Pregnancy and Nursing Mothers:** Quetiapine should be used only if the potential benefit justifies the potential risk. (8.1) Breast feeding is not recommended. (8.3)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)

—SEE 17 FOR PATIENT COUNSELING INFORMATION —

Revised 11/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: 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. Analyses of seventeen placebo-controlled trials (modal 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 appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL XR is not approved for the treatment of patients with Dementia-Related Psychosis.

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL XR is not approved for use in pediatric patients. SEROQUEL XR is not approved for use in the treatment of depression, however, an immediate release form of quetiapine (SEROQUEL) is approved for the treatment of bipolar depression.

1 INDICATIONS AND USAGE

SEROQUEL XR is indicated for the acute and maintenance treatment of schizophrenia [*see Clinical Studies* (14.1)].

The efficacy of SEROQUEL XR in schizophrenia was established in part, on the basis of extrapolation from the established effectiveness of SEROQUEL. In addition, the efficacy of SEROQUEL XR was demonstrated in 1 short-term (6-week) controlled trial of schizophrenic inpatients and outpatients [*see Clinical Studies* (14.1)]. The longer-term benefit of maintaining patients on monotherapy with SEROQUEL XR after achieving a responder status for 16 weeks was demonstrated in a controlled trial [*see Clinical Studies* (14.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dose

SEROQUEL XR should be administered once daily, preferably in the evening. The recommended initial dose is 300 mg/day. Patients should be titrated within a dose range of 400 – 800 mg/day depending on the response and tolerance of the individual patient [*see Clinical Studies* (14)]. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

SEROQUEL XR tablets should be swallowed whole and not split, chewed or crushed.

It is recommended that SEROQUEL XR be taken without food or with a light meal (approximately 300 calories) [*see Clinical Pharmacology* (12.3)].

2.2 Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions [*see Use in Specific Populations* (8.5 and 8.7) *and Clinical Pharmacology* (12)]. When indicated, dose escalation should be performed with caution in these patients.

For those patients who require less than 200 mg per dose of SEROQUEL XR during the initial titration, use the immediate release formulation.

Elderly patients should be started on SEROQUEL immediate release formulation 25 mg/day and the dose can be increased in increments of 25-50 mg/day depending on the response and tolerance of the individual patient. When an effective dose has been reached, the patient may be switched to SEROQUEL XR at an equivalent total daily dose [*see Dosage and Administration* (2.5)].

Patients with hepatic impairment should be started on SEROQUEL immediate release formulation 25 mg/day. The dose can be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerance of the patient. When an effective dose has been reached, the patient may be switched to SEROQUEL XR at an equivalent total daily dose [*see Dosage and Administration* (2.5)].

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital [*see Drug Interactions* (7.1)].

2.3 Maintenance Treatment

While there is no body of evidence available to specifically address how long the patient treated with SEROQUEL XR should remain on it, a longer-term study with SEROQUEL XR has shown this drug to be effective in delaying time to relapse in patients who were stabilized on SEROQUEL XR at doses of 400 to 800 mg/day for 16 weeks [*see Clinical Studies* (14.1)]. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [*See Clinical Studies* (14.1)].

2.4 Re-initiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting therapy of patients who have been off SEROQUEL XR for more than one week, the initial dosing schedule should be followed. When restarting patients who have been off SEROQUEL XR for less than one week, gradual dose escalation may not be required and the maintenance dose may be reinitiated.

2.5 Switching Patients from SEROQUEL Tablets to SEROQUEL XR Tablets

Schizophrenic patients who are currently being treated with divided doses of SEROQUEL (immediate release formulation, eg, 2 to 3 times per day) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

2.6 Switching from Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to SEROQUEL XR, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL XR therapy in place of the next scheduled injection. The need for continuing existing extrapyramidal syndrome medication should be re-evaluated periodically.

3 DOSAGE FORMS AND STRENGTHS

200 mg extended-release tablets
300 mg extended-release tablets
400 mg extended-release tablets

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 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 XR (quetiapine fumarate) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).

5.2 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation

and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. 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.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SEROQUEL XR is not approved for use in treating depression, however, an immediate release form of quetiapine (SEROQUEL) is approved for the treatment of bipolar depression.

5.3 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine. [*see Adverse Reactions, Hyperglycemia* (6.2)] 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 reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions 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 anti-diabetic treatment despite discontinuation of the suspect drug.

5.4 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 quetiapine. Rare cases of NMS have been reported with quetiapine. Clinical manifestations of NMS are hyperpyrexia, 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 reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

5.5 Orthostatic Hypotension

Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its á1-adrenergic antagonist properties. Syncope was reported in 0.3% (3/951) of the patients treated with SEROQUEL XR, compared with 0.3% (1/319) on placebo. Syncope was reported in 1% (23/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/527) on placebo.

Quetiapine 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 patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

5.6 Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including quetiapine fumarate. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. 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 XR at the first sign of a decline in WBC in absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue SEROQUEL XR and have their WBC followed until recovery [*see Adverse Reactions* (6.2)].

5.7 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic 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 the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, quetiapine 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 dose 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 quetiapine, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome.

5.8 Cataracts

The development of cataracts was observed in association with quetiapine treatment in chronic dog studies *[see Animal Toxicology* (13.2)]. Lens changes have also been observed in patients during long-term quetiapine treatment, but a causal relationship to quetiapine use has not been established. Nevertheless, the possibility of lenticular changes 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.

5.9 Seizures

During clinical trials with SEROQUEL XR, seizures occurred in 0.1% (1/951) of patients treated with SEROQUEL XR compared to 0.9% (3/319) on placebo. During clinical trials with SEROQUEL, seizures occurred in 0.5% (20/3490) patients treated with SEROQUEL compared to 0.2% (2/954) on placebo. As with other antipsychotics quetiapine

should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.10 Hypothyroidism

In SEROQUEL XR clinical trials, 0.5% (4/806) of patients on SEROQUEL XR vs. 0% (0/262) on placebo experienced decreased free thyroxine and 2.7% (21/786) on SEROQUEL XR vs. 1.2% (3/256) on placebo experienced increased TSH; however, no patients experienced a combination of clinically significant decreased free thyroxine and increased TSH. No patients had reactions of hypothyroidism. 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 TBG were unchanged. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of these patients with TSH increases needed replacement thyroid treatment.

5.11 Cholesterol and Triglyceride Elevations

In schizophrenia clinical trials, SEROQUEL XR treated patients had increases from baseline in mean cholesterol and triglycerides of 4% and 15%, respectively compared to decreases from baseline in mean cholesterol and triglycerides of 2% and 6% for placebo treated patients. In schizophrenia clinical trials, SEROQUEL treated patients had increases from baseline in mean cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients.

5.12 Hyperprolactinemia

An elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL XR as compared with placebo. Increased prolactin levels with quetiapine were observed in rat toxicity studies, and were associated with an increase in mammary gland

neoplasia in rats. [*see Carcinogenesis, Mutagenesis, Impairment of Fertility* (13.1)]. 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.

5.13 Transaminase Elevations

Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of 6-week placebo controlled schizophrenia trials were approximately 1% for SEROQUEL XR compared to 2% for placebo. 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. 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.

5.14 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event reported in patients treated with quetiapine especially during the 3-day period of initial dose titration. In schizophrenia trials, somnolence and sedation were reported in 12% and 13% of patients on SEROQUEL XR respectively compared to 4% and 7% of placebo patients. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since quetiapine 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 quetiapine therapy does not affect them adversely.

5.15 Priapism

One case of priapism in a patient receiving quetiapine was reported prior to market introduction. While a causal relationship to use of quetiapine has not been established, other drugs with α-adrenergic blocking effects have been reported to induce priapism, and it is

possible that quetiapine may share this capacity. Severe priapism may require surgical intervention.

5.16 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL XR 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.

5.17 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 XR and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.18 Suicide

The possibility of a suicide attempt is inherent in schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL XR should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In three, 6-week clinical studies in patients with schizophrenia (N=951) the incidence of treatment emergent suicidal ideation or suicide attempt, as measured by the Columbia Analysis of Suicidal Behavior, was low in SEROQUEL XR treated patients (0.6%) and similar to placebo (0.9%).

5.19 Use in Patients with Concomitant Illness

Clinical experience with SEROQUEL XR in patients with certain concomitant systemic illnesses [*see Pharmacokinetics* (12.3)] is limited.

SEROQUEL XR 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 XR, caution

should be observed in cardiac patients [*see Warnings and Precautions* (5.5)].

5.20 Withdrawal

Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including quetiapine. Gradual withdrawal is advised.

6 ADVERSE REACTIONS

6.1. Clinical Studies 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 XR consisting of 951 patients exposed to SEROQUEL XR for the treatment of schizophrenia in placebo controlled trials. This experience corresponds to approximately 82.9 patient-years. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, body weights, laboratory analyses, and ECG results.

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 event categories. In the tables and tabulations that follow, standard MedDRA terminology has been used to classify reported adverse reactions.

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. An event 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

There was no difference in the incidence and type of adverse reactions associated with discontinuation (6.4% for SEROQUEL XR vs. 7.5% for placebo) in a pool of controlled trials.

Adverse Reactions Occurring at an Incidence of 5% or More Among SEROQUEL XR Treated Patients in Short-Term, Placebo-Controlled Trials

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) in ≥ 5% patients treated with SEROQUEL XR (doses ranging from 300 to 800 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

Table 2. Treatment-Emergent Adverse Reaction Incidence in 6-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia

Body System/Preferred Term	SEROQUEL XR (n=951)	PLACEBO (n=319)
Gastrointestinal Disorders		
Dry mouth	12%	1%
Constipation	6%	5%
Dyspepsia	5%	2%
Nervous System Disorders		
Sedation	13%	7%
Somnolence	12%	4%
Dizziness	10%	4%
Vascular Disorders		
Orthostatic hypotension	7%	5%

[1]Reactions for which the SEROQUEL XR incidence was equal to or less than placebo are not listed in the table, but included the following: headache, insomnia, and nausea.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were dry mouth (12%), somnolence (12%), dizziness (10%), and dyspepsia (5%).

Adverse Reactions Occurring at an Incidence of 5% or More Among SEROQUEL XR Treated Patients in Long-Term, Placebo-Controlled Trials

In a longer-term placebo-controlled trial, adult patients with schizophrenia who remained clinically stable on SEROQUEL XR during open label treatment for at least 4 months were randomized to placebo (n=103) or to continue on their current SEROQUEL XR (n=94) for up to 12 months of observation for possible relapse, the adverse reactions reported were generally consistent with those reported in the short-term, placebo-trials. Insomnia (8.5%) and headache (7.4%) were the only adverse events reported by 5% or more patients.

Adverse Reactions that occurred in <5% of patients and were considered drug-related (incidence greater than placebo and consistent with known pharmacology of drug class) in order of decreasing frequency:

heart rate increased, hypotension, weight increased, tremor, akathisia, increased appetite, blurred vision, postural dizziness, pyrexia, dysarthria, dystonia, drooling, syncope, tardive dyskinesia, dysphagia, leukopenia, and rash.

Adverse Reactions that have historically been associated with the use of SEROQUEL and not listed elsewhere in the label

The following adverse reactions have also been reported with SEROQUEL: anaphylactic reaction, peripheral edema, rhinitis, eosinophilia, hypersensitivity, elevations in gamma-GT levels and restless legs syndrome.

Extrapyramidal Symptoms:

Four methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) Barnes Akathisia Rating Scale (BARS) Global

Assessment Score (3) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (4) use of anticholinergic medications to treat emergent EPS.

In three-arm placebo-controlled clinical trials for the treatment of schizophrenia, utilizing doses between 300 mg and 800 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 8% for SEROQUEL XR and 8% for SEROQUEL (without evidence of being dose related), and 5% in the placebo group. In these studies, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, and muscle rigidity) was generally low and did not exceed 3% for any treatment group.

At the end of treatment, the mean change from baseline in SAS total score and BARS Global Assessment score was similar across the treatment groups. The use of concomitant anticholinergic medications was infrequent and similar across the treatment groups. The incidence of extrapyramidal symptoms was consistent with that seen with the profile of SEROQUEL in schizophrenia patients.

6.2 Vital Signs and Laboratory Studies

Vital Sign Changes:

Quetiapine is associated with orthostatic hypotension [*see Warnings and Precautions* (5.5)].

Weight Gain:

In schizophrenia trials with SEROQUEL XR, the proportions of patients meeting a weight gain criterion of ≥7% of body weight was 10% for SEROQUEL XR compared to 5% for placebo. In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significant greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Laboratory Changes:

An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in ALT and increases in both total cholesterol and triglycerides [*see Warnings and Precautions* (5.11; 5.13)]. In post-marketing clinical

trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed.

In three-arm SEROQUEL XR placebo controlled monotherapy clinical trials, among patients with a baseline neutrophil count ≥ 1.5 X 10^9/L, the incidence of at least one occurrence of neutrophil count <1.5 X 10^9/L was 1.5% in patients treated with SEROQUEL XR and 1.5% for SEROQUEL, compared to 0.8% in placebo-treated patients.

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 x 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 XR at the first sign of a decline in WBC in absence of other causative factors [*see Warnings and Precautions* (5.6].

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 (≥ 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 ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine fumarate 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 ≥200 mg/dl was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥ 126 mg/dl was 2.6%.

ECG Changes:
0.8% of SEROQUEL XR patients, and no placebo patients, had tachycardia (>120 bpm) at any time during the trials. SEROQUEL XR was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean decrease of 1 beat per minute for placebo. This is consistent with the rates of SEROQUEL. The incidence of adverse reactions of tachycardia was 3% for SEROQUEL XR compared to 1% 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. The slight tendency for tachycardia may be related to quetiapine's potential for inducing orthostatic changes [*see Warnings and Precautions* (5)].

6.3 Post Marketing Experience:
The following adverse reactions were identified during post approval use of SEROQUEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction which were temporally related to SEROQUEL therapy include: anaphylactic reaction, and restless legs.

Other adverse reactions reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy hyponatremia, myocarditis rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Stevens-Johnson syndrome (SJS).

7 DRUG INTERACTIONS

The risks of using SEROQUEL XR in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL XR, caution should be used when it is taken in combination with other centrally acting drugs.

Quetiapine potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be limited while taking quetiapine.

Because of its potential for inducing hypotension, SEROQUEL XR may enhance the effects of certain antihypertensive agents.

SEROQUEL XR may antagonize the effects of levodopa and dopamine agonists.

7.1 The Effect of Other Drugs on Quetiapine

Phenytoin

Coadministration of quetiapine (250 mg three times/day) and phenytoin (100 mg three times /day) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL XR 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, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, valproate) [*see Dosage and Administration* (2)].

Divalproex

Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady-state by 17% without affecting the extent of absorption or mean oral clearance.

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 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

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 335% increase in maximum plasma concentration

of quetiapine. Caution (reduced dosage) is indicated when SEROQUEL XR is administered with ketoconazole and other inhibitors of cytochrome P450 3A (eg, itraconazole, fluconazole, erythromycin, protease inhibitors).

Fluoxetine, Imipramine, Haloperidol, and Risperidone

Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

7.2. Effect of Quetiapine on Other Drugs

Lorazepam

The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Divalproex

The mean maximum concentration and extent of absorption of total and free valproic acid at steady-state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant.

Lithium

Concomitant administration 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 (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed 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/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal 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/m^2 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.

8.2 Labor and Delivery

The effect of SEROQUEL XR on labor and delivery in humans is unknown.

8.3 Nursing Mothers

SEROQUEL XR was excreted in milk of treated animals during lactation. It is not known if SEROQUEL XR is excreted in human milk. It is recommended that women receiving SEROQUEL XR should not breast feed.

8.4 Pediatric Use

The safety and effectiveness of SEROQUEL XR in pediatric patients have not been established.

8.5 Geriatric Use

Sixty-eight patients in clinical studies with SEROQUEL XR were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL XR in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL XR, or cause poorer tolerance or orthostasis, 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 quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients [*see Use in Special Populations* (2.2) *and Pharmacokinetics* (12.3)].

8.6 Renal Impairment

Clinical experience with SEROQUEL XR in patients with renal impairment [*see Clinical Pharmacology* (12.3)] is limited.

8.7 Hepatic Impairment

Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed [*see Dosing and Administration* (2.2) *and Clinical Pharmacology* (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

SEROQUEL XR is not a controlled substance.

9.2 Abuse

SEROQUEL XR 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 any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, 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 XR, (eg, development of tolerance, increases in dose, drug-seeking behaviour).

10 OVERDOSAGE

10.1 Human Experience

In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose [*see Warnings and Precautions* (5.4)]. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation.

10.2 Management of Overdosage

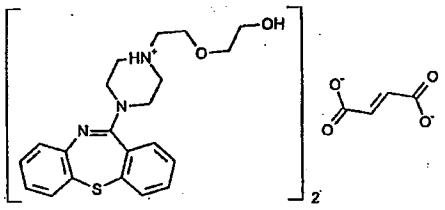
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction 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 antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL XR. Similarly it is reasonable to expect that the α-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL XR. Therefore, appropriate supportive measures should be instituted. 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 β stimulation may worsen hypotension in the setting of quetiapine-induced α blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

SEROQUEL XR (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo [*b,f*] [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL XR is supplied for oral administration as 200 mg (yellow), 300 mg (pale yellow), and 400 mg (white). All tablets are capsule shaped and film coated.

Inactive ingredients for SEROQUEL XR are, lactose monohydrate, microcrystalline cellulose, sodium citrate, hypromellose, and magnesium stearate. The film coating for all SEROQUEL XR tablets contain hypromellose, polyethylene glycol 400 and titanium dioxide. In addition yellow iron oxide (200 and 300 mg tablets) are included in the film coating of specific strengths.

Each 200 mg tablet contains 230 mg of quetiapine fumarate equivalent to 200 mg quetiapine. Each 300 mg tablet contains 345 mg of quetiapine fumarate equivalent to 300 mg quetiapine. Each 400 mg tablet contains 461 mg of quetiapine fumarate equivalent to 400 mg quetiapine.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of quetiapine, as with other drugs having efficacy in the treatment of schizophrenia, is unknown. However, it is believed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism, by quetiapine and its active metabolite N-desalkyl quetiapine.

Antagonism at receptors other than dopamine D_2 and serotonin $5HT_2$ with similar or greater affinities may explain some of the other effects of quetiapine and N-desalkyl quetiapine; antagonism at histamine H_1 receptors may explain the somnolence and antagonism at adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

12.2 Pharmacodynamics

Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT1_A$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM respectively), histamine H1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). Quetiapine has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

12.3 Pharmacokinetics

Following multiple dosing of quetiapine up to a total daily dose of 800 mg, administered in divided doses, the plasma concentration of quetiapine and N-desalkyl quetiapine, the major active metabolite of quetiapine, were proportional to the total daily dose. Accumulation is predictable upon multiple dosing. Steady-state mean C_{max} and AUC of N-desalkyl quetiapine are about 21-27% and 46-56%, respectively of that observed for quetiapine. Elimination of quetiapine is mainly via hepatic metabolism. The mean-terminal half-life is approximately 7 hours for quetiapine and 9 to 12 hours for N-desalkyl quetiapine within the clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. SEROQUEL XR is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption

Quetiapine fumarate reaches peak plasma concentrations approximately 6 hours following administration. SEROQUEL XR dosed once daily at steady-state has comparable bioavailability to an equivalent total daily dose of SEROQUEL administered in divided doses, twice daily. A high-fat meal (approximately 800 to 1000 calories) was found to produce statistically significant increases in the SEROQUEL XR C_{max} and AUC of 44% to 52% and 20% to 22%, respectively, for the 50-mg and 300-mg tablets. In comparison, a light meal (approximately 300 calories) had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that SEROQUEL XR be taken without food or with a light meal [*see Dosage and Administration* (2)].

Distribution

Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination

Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively. The average dose fraction of free quetiapine and its major active metabolite is <5% excreted in the urine.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite and in the metabolism of its active metabolite N-desalkyl quetiapine.

Gender

There is no gender effect on the pharmacokinetics of quetiapine.

Race
There is no race effect on the pharmacokinetics of quetiapine.

Smoking
Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency
Patients with severe renal impairment (CL_{cr}=10-30 mL/min/1.73m^2, n=8) had a 25% lower mean oral clearance than normal subjects (CL_{cr}>80 mL/min/1.73m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency
Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In 2 of the 8 hepatically impaired patients, AUC and C_{max} were 3 times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed [*see Dosage and Administration* (2)].

Drug-Drug Interactions
In vitro enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole [*see Drug Interactions* (7.1) *and Dosage and Administration* (2)].

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam [*see Drug Interactions* (7.2)].

13 NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (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/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 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/m^2 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 subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell 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-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- 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 considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown [*see Warnings and Precautions* (5.12)].

Mutagenesis

The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* 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 oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug related effects included increases in interval to mate 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/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 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/m^2 basis. The no effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

13.2 Animal Toxicology and/or Pharmacology

Quetiapine caused 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; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 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 effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 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 cataracts in individual dogs. The appearance of delta 8 cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of SEROQUEL XR in the treatment of schizophrenia was demonstrated in 1 short-term, 6-week, fixed-dose, placebo-controlled trial of inpatients and outpatients with schizophrenia (n=573) who met DSM IV criteria for schizophrenia. SEROQUEL XR (once daily) was administered as 300 mg on (Day 1), and the dose was increased to either 400 mg or 600 mg by Day 2, or 800 mg by Day 3. The primary endpoint was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment (Day 42). SEROQUEL XR doses of 400 mg, 600 mg and 800 mg once daily were superior to placebo in the PANSS total score at Day 42.

In a longer-term trial, clinically stable adult outpatients (n=171) meeting DSM-IV criteria for schizophrenia who remained stable following 16 weeks of open label treatment with flexible doses of SEROQUEL XR (400-800 mg/day) were randomized to placebo or to continue on their current SEROQUEL XR (400-800 mg/day) for observation for possible relapse during the double-blind continuation (maintenance) phase.

Stabilization during the open label phase was defined as receiving a stable dose of SEROQUEL XR and having a CGI-S≤4 and a PANSS score ≤60 from beginning to end of this open-label phase (with no increase of ≥10 points in PANSS total score). Relapse during the double-blind phase was defined in terms of a ≥30% increase in the PANSS Total score, or CGI-Improvement score of ≥6, or hospitalization due to worsening of schizophrenia, or need for any other antipsychotic medication. Patients on SEROQUEL XR experienced a statistically significant longer time to relapse than did patients on placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

- 200 mg Tablets (NDC 0310-0282) yellow, film coated, capsule-shaped, biconvex, intagliated tablet with "SR 200" on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.

- 300 mg Tablets (NDC 0310-0283) pale yellow, film coated, capsule-shaped, biconvex, intagliated tablet with "SR 300" on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.

- 400 mg Tablets (NDC 0310-0284) white, film coated, capsule-shaped, biconvex, intagliated tablet with "SR 400" on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.

Store SEROQUEL XR at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

17 PATIENT COUNSELING INFORMATION

Hyperglycemia and Diabetes Mellitus

Patients should be advised of the symptoms of hyperglycemia (high blood sugar, polydipsia, polyuria, polyphagia, and weakness) and be advised regarding the risk of diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should be monitored [*see Warning and Precautions* (5.3)].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. Quetiapine is not approved for elderly patients with dementia-related psychosis [*see Warning and Precautions* (5.1)].

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [*see Warning and Precautions* (5.2)].

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for SEROQUEL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document. It should be noted that SEROQUEL XR is not approved for treatment of depression, however, an immediate release form of quetiapine (SEROQUEL) is approved for the treatment of bipolar depression.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing) especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose [*see Warning and Precautions* (5.5)].

Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL XR [*see Warning and Precautions* (5.6)].

Interference with Cognitive and Motor Performance

Patients should be advised of the risk of somnolence or sedation, especially during the period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating machinery, until they are reasonably certain quetiapine therapy does not affect them adversely. Patients should limit consumption of alcohol during treatment with quetiapine [*see Warning and Precautions* (5.14)].

Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised not to breast feed if they are taking quetiapine [*see Use in Special Populations* (8.3)].

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.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Neuroleptic Malignant Syndrome (NMS)

Patients should be advised to report to their physician any signs or symptoms that may be related to NMS. These may include muscle stiffness and high fever [*see Warning and Precautions* (5.4)].

Medication Guide

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**

2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide

- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.

- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

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

It should be noted that SEROQUEL XR is not approved for treatment of depression, however, an immediate release form of quetiapine (Seroquel) is approved for the treatment of bipolar depression.

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Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Made in United Kingdom