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FDA Approves Seroquel XR For Add-On Treatment of Major Depressive Disorder

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WILMINGTON, Del., Dec. 4 /PRNewswire-FirstCall/ -- AstraZeneca today announced that the US Food and Drug Administration (FDA) has approved once-daily Seroquel XR (quetiapine fumarate) Extended Release Tablets as adjunctive (add-on) treatment to antidepressants in adults with Major Depressive Disorder (MDD). Seroquel XR is the only medication in its class approved by the FDA to treat both major depressive disorder as adjunctive therapy and acute depressive episodes associated with bipolar disorder as monotherapy.(1)(2)

MDD affects approximately 14.2 million American adults in a given year, and today it is often treated with antidepressants(3). Selective serotonin reuptake inhibitors, or SSRIs, are among the most commonly prescribed class of antidepressant medications for depression; however, in many cases patients fail to respond adequately to treatment(4). Results from a National Institute of Mental Health study, STAR*D, showed that approximately 63% of patients did not achieve remission with the SSRI citalopram when used as a first-line treatment(4). Additionally, this study reported that overall approximately one-third of patients with MDD failed to achieve study defined remission(4). This approval for Seroquel XR provides physicians with a new adjunctive treatment option for patients with MDD who have an inadequate response to their current antidepressant.

In addition to the FDA approval for the adjunctive indication in MDD, AstraZeneca has received a Complete Response Letter (CRL) from the FDA asking for additional information for the sNDAs for Seroquel XR as acute monotherapy and maintenance monotherapy for the treatment of MDD in adult patients.

AstraZeneca is evaluating the contents of the CRL. AstraZeneca will continue discussions with the FDA and will provide a response to the agency in due course. The CRL does not change the current recommendations for the treatment of patients taking Seroquel XR for approved indications in schizophrenia and bipolar disorder.

The FDA has required that AstraZeneca implement a Risk Evaluation and Mitigation Strategy (REMS). The REMS for Seroquel XR requires a Medication Guide and periodic assessments that will include a survey of patients' understanding of the potential risks of Seroquel XR. The REMS applies to all approved indications.

"Many people with major depressive disorder, despite being treated with currently approved medications, continue to experience depressive symptoms," said Dr. Richard Weisler(*). Adjunct Professor of Psychiatry at University of North Carolina School of Medicine and Adjunct Associate Professor at Duke University Medical Center. "Seroquel XR may provide another effective treatment option for the depressive symptoms

associated with MDD as adjunctive treatment to antidepressants."

"Today's FDA approval of Seroquel XR is based on a clinical development program in MDD involving 939 patients randomized across two studies that assessed the efficacy and safety of once-daily treatment with Seroquel XR as adjunctive treatment to antidepressants," said Lisa Schoenberg, VP Specialty Care, AstraZeneca. "This new indication for Seroquel XR marks an important milestone in the treatment of MDD, as there is a significant need for additional options that may help patients with this devastating condition who are not adequately responding to their antidepressant therapy."

Seroquel XR is part of a class of drugs called atypical antipsychotics and is approved for a number of mental health disorders. In addition to today's approval for the adjunctive treatment of MDD, Seroquel XR is currently approved for the acute and maintenance treatment of bipolar disorder and schizophrenia.

Major Depressive Disorder sNDA Submission

The FDA approval of Seroquel XR for MDD was based on a supplemental new drug application (sNDA) comprising findings from two Phase III, placebo-controlled studies that assessed the efficacy and safety of once-daily treatment with Seroquel XR as adjunctive treatment in patients with MDD. Studies 6 and 7 were acute adjunctive therapy studies (with ongoing antidepressant therapy) involving 939 patients randomized (628 randomized to Seroquel XR) who had an inadequate response to their antidepressant therapy(5,6). Patients were on various antidepressants prior to study entry including SSRI's (paroxetine, fluoxetine, sertraline, escitalopram, or citalopram), SNRI's (duloxetine and venlafaxine), TCA (amitryptiline) and other (buproprion)(1).

The primary endpoint in these studies was the change from baseline to end of treatment in the Montgomery-Asberg Depression Rating Scale(MADRS)(**) total score. The recommended dose range of Seroquel XR in MDD is 150 to 300mg/day(5,6).

In both studies efficacy with Seroquel XR was superior to placebo, as assessed by the primary endpoints(1). Seroquel XR 300 mg once daily as adjunctive treatment to other antidepressant therapy was superior to antidepressant alone in reduction of MADRS total score in both trials. Seroquel XR 150 mg once daily as adjunctive treatment was superior to antidepressant therapy alone in reduction of MADRS total score in one trial. In these studies, the most commonly observed adverse reactions associated with the use of Seroquel XR (incidence of 5% or greater and at least twice that of placebo) were somnolence (150 mg: 37%, 300 mg: 43%), dry mouth (150 mg: 27%, 300 mg 40%), fatigue (150 mg: 14%, 300 mg: 11%) and constipation (150 mg only: 11%)(1). The adverse events seen with Seroquel XR in these studies were generally consistent with the known profile of Seroquel XR in other indications(5,6).

About Major Depressive Disorder

MDD affects approximately 14.2 million American adults in a given year and today it is often treated with antidepressants(3). Unlike normal instances of sadness, loss, or passing mood states, MDD is persistent and can interfere with an individual's thoughts, behavior, mood, activity, and physical health. Depression is one of

the leading causes of disability in the US(8).

Symptoms of depression include: persistently sad or irritable mood; pronounced changes in sleep, appetite, and energy; difficulty thinking, concentrating, and remembering; physical slowing or agitation; lack of interest in or pleasure from activities that were once enjoyed; feelings of guilt, worthlessness, hopelessness, and emptiness; recurrent thoughts of death or suicide(9). The diagnostic criteria for a major depressive episode in MDD is the same as a depressive episode of bipolar disorder with the major distinguishing feature between the disorders being the absence of manic or hypomanic episodes in MDD(9).

Seroquel XR Regulatory Milestones

Seroquel XR, a once-daily, extended-release formulation of quetiapine fumarate, was approved in the US in 2007 for the treatment of schizophrenia in adult patients and in October 2008 for the acute treatment of the depressive episodes associated with bipolar disorder, the manic and mixed episodes associated with bipolar I disorder, and the maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex.

Important Safety Information for Seroquel XR

Seroquel XR is indicated for the treatment of major depressive disorder, as adjunctive treatment to antidepressants in adults with major depressive disorder; the acute treatment of depressive episodes in bipolar disorder; acute manic or mixed episodes in bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex; for the maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex; and the treatment of schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment and the appropriate dose.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death, compared to placebo (4.5% vs 2.6%, respectively). Seroquel XR is not approved for the treatment of patients with dementia-related psychosis. (See Boxed Warning.)

Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Patients of all ages started on therapy should be 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 patients under the age of 18 years. (See Boxed Warning.)

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 management of NMS should include immediate discontinuation of antipsychotic drugs.

Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including quetiapine. The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics. Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

Undesirable alterations in lipids have been observed with Seroquel XR use. Increases in total cholesterol, LDL-cholesterol and triglycerides, and decreases in HDL-cholesterol have been reported in clinical trials. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of and periodically during treatment.

Increases in weight have been observed in clinical trials. Patients receiving Seroquel XR should receive regular monitoring of weight.

Leukopenia, neutropenia, and agranulocytosis (including fatal cases), have been reported temporally related to atypical antipsychotics, including quetiapine. Patients with a pre-existing low white blood cell (WBC) count or a history of drug induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy. In these patients, Seroquel XR should be discontinued at the first sign of a decline in WBC absent other causative factors. Patients with neutropenia should be carefully monitored, and Seroquel XR should be discontinued in any patient if the absolute neutrophil count is <1000/mm(3).

Tardive dyskinesia (TD), a potentially irreversible syndrome of involuntary dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic drugs administered to the patient increase. TD may remit, partially or completely, if antipsychotic treatment is withdrawn. Quetiapine should be prescribed in a manner that is most likely to minimize the occurrence of TD.

Warnings and Precautions also include the risk of orthostatic hypotension, cataracts, seizures, hyperprolactinemia, and dysphagia. 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. The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high risk patients should accompany drug therapy.

The most commonly observed adverse reactions associated with the use of Seroquel XR versus placebo in clinical trials for major depressive disorder, schizophrenia and bipolar disorder were: somnolence (25-52% vs

9-13%), dry mouth (12-40% vs 1-8%), constipation (6-11% vs 3-6%), dizziness (10-13% vs 4-11%), increased appetite (2-12% vs 0-6%), dyspepsia (2-7% vs 1-4%), weight gain (3-7% vs 0-1%), fatigue (3-14% vs 2-4%), dysarthria (1-5% vs 0%), and nasal congestion (2-5% vs 1%).

Please see Prescribing Information for Seroquel XR, including Boxed Warnings.

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The statements contain herein include forward-looking statements. Although we believe our expectations are based on reasonable assumptions, any forward-looking statements, by their very nature, involve risks and uncertainties and may be influenced by factors that could cause actual outcomes and results to be materially different from those predicted. The forward-looking statements reflect knowledge and information available at the date of the preparation of this press release and the Company undertakes no obligation to update these forward-looking statements. Important factors that could cause actual results to differ materially from those contained in forward-looking statements, certain of which are beyond our control, include, among other things, those risk factors identified in the Company's Annual Report/Form 20-F for 2008. Nothing contained herein should be construed as a profit forecast.

(*) Dr. Weisler provides services to AstraZeneca as a consultant, speaker and research investigator

(**) Montgomery-Asberg Depression Rating Scale: a 10-item scale that measures severity of symptoms on a scale of 0 to 6(7).

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CONTACT: Kirsten Evraire, +1-302-885-0435, **kirsten.evraire@astrazeneca.com**, Shannon Miller, +1-302-885-3623, **shannon.miller@astrazeneca.com**, both of AstraZeneca

Web Site: **http://www.astrazeneca-us.com/**

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