AstraZeneca

**Advisory Committee Briefing Document**

Drug substance: quetiapine fumarate extended release (XR)

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# SEROQUEL XR™ (quetiapine fumarate) Extended-Release Tablets for the Treatment of Patients with either Major Depressive Disorder or Generalized Anxiety Disorder

## Briefing Document for Psychopharmacologic Drugs Advisory Committee Meeting of April 8, 2009, Related to Supplemental NDAs (NDA 22-047/S-010/S-011/S-012) and (NDA 20-047/S-014/S-015)

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# EXECUTIVE SUMMARY

AstraZeneca submitted supplemental New Drug Applications (sNDA) for SEROQUEL XR (quetiapine XR) for Major Depressive Disorder (MDD) as monotherapy, adjunct, and maintenance treatment. Subsequently, supplements for quetiapine XR were submitted for Generalized Anxiety Disorder (GAD) as monotherapy and maintenance treatment.

The question before this Advisory Committee is whether quetiapine XR, with appropriate labeling and patient risk management, should be approved as a treatment option for patients with MDD or GAD.

This briefing document outlines the benefit-risk profile of low doses of quetiapine XR (50 to 300 mg/day) in these indications. The document is based on:

- ***Extensive clinical development programs in MDD and GAD, which included 6816 patients.*** Of these MDD and GAD patients, 519 were exposed for at least 6 months, and 123 for at least 12 months.

- ***Existing understanding of quetiapine gained through postmarketing experience and clinical studies in schizophrenia and bipolar disorder.*** An estimated 22 million patients worldwide have received quetiapine since first approval in 1997, and approximately 26,000 subjects have been exposed to quetiapine and quetiapine XR in 118 clinical studies to date.

AstraZeneca believes that quetiapine XR offers an important new treatment option for patients with MDD and GAD and that, with appropriate labeling and risk management, the benefits outweigh the risks. This view is based on the following considerations:

- ***There remains an unmet need in both MDD and GAD despite the existence of multiple approved therapies.*** Both disorders are associated with significant levels of morbidity and mortality, including suicide, and often co-exist with other medical and psychiatric disorders, which further complicates diagnosis and treatment. Thus these disorders exert a tremendous toll on affected individuals, their families, and society. Despite the availability of a number of treatment options, many patients remain intolerant to side effects, have an inadequate response, or fail to achieve disease remission with existing treatments. These factors contribute to more than 50% of patients not achieving disease remission. In attempting to address this unmet need, clinicians select antidepressants based upon the avoidance of specific side effects and the presence of comorbid psychiatric disorders, specific clinical symptoms and existing underlying medical conditions. For these reasons, no one treatment can be considered suitable for all patients: a broad range of treatment options is required, and additional treatment options are needed to supplement current therapies.

- ***Quetiapine XR provides an alternative treatment approach to existing approved therapies.*** Current treatment guidelines, such as those of the American Psychiatric Association, recommend that alternative treatments should be considered if a patient experiences a problematic side-effect or has an inadequate response to treatment. They also recommend consideration of an antidepressant from a different class if two previous medication studies from the same class were ineffective. In the treatment of MDD and GAD, quetiapine XR offers a treatment with a different mechanism of action, demonstrating a fast onset of efficacy and a different tolerability profile to currently marketed antidepressants. Recent research has shown that the mechanism of action of quetiapine XR is distinctive from available treatment options because it combines a well established antidepressant mechanism, norepinephrine reuptake inhibition, with serotonergic and dopaminergic mechanisms not demonstrated in any other approved drug. As well as offering an alternative mechanism of action by which to treat MDD and GAD, quetiapine XR is an approved treatment for bipolar depression and bipolar mania. It is estimated that 35 to 45% of patients with bipolar depression are initially misdiagnosed with MDD. Treatment of these patients with certain established antidepressants can induce mania or hypomania.

- ***Quetiapine XR at low doses (50 to 300 mg/day) is an efficacious antidepressant in MDD.*** In MDD, robust efficacy of quetiapine XR has been demonstrated in 7 out of 8 well controlled studies, including 3 of 4 monotherapy studies, 2 adjunct studies, 1 elderly study, and 1 long-term maintenance (randomized withdrawal) study. Efficacy was demonstrated in MDD patients with moderate to severe depressive symptoms (as for established antidepressants). Efficacy was also demonstrated as an adjunctive therapy with an antidepressant in patients who have had an inadequate response to antidepressant treatment alone (as for aripiprazole, Abilify®). Quetiapine XR demonstrated an early improvement of symptoms (by Week 1) in studies in contrast to many existing treatments. Maintenance of efficacy was demonstrated in long-term treatment. The FDA accepts that efficacy has been demonstrated in patients with MDD.

- ***Quetiapine XR at low doses (50 to 300 mg/day) is an efficacious anxiolytic in GAD.*** In GAD, robust efficacy of quetiapine XR has been demonstrated in all 5 studies: 3 monotherapy studies, 1 elderly study, and 1 long-term maintenance (randomized withdrawal) study. Efficacy findings included alleviating anxiety symptoms, as measured by change in the Hamilton Rating Scale for Anxiety (HAM-A) score from baseline to end of randomization, as for established agents approved for the treatment of GAD. Additionally symptom improvement was seen as early as Day 4, and efficacy was maintained during long-term treatment. The FDA accepts that efficacy has been demonstrated in patients with GAD.

- ***The general safety profile of quetiapine is well characterized.*** This profile is based on clinical investigation in schizophrenia, bipolar disorder, MDD, and GAD. It is estimated that over 22 million patients worldwide have been treated since

quetiapine was first approved. Approximately 26,000 subjects have been exposed to quetiapine and quetiapine XR in 118 clinical studies to date. This population includes pediatric and elderly patients. The US Prescribing Information (USPI) for both formulations alerts prescribers to Warnings and Precautions concerning the use of atypical antipsychotics in general and quetiapine specifically. Also the most common adverse events (AEs) are described in the label.

- ***The overall safety profile of quetiapine XR in the treatment of MDD and GAD is consistent with the known safety profile of quetiapine.*** No additional safety findings were seen at the doses (50 to 300 mg/day) used in these patient populations. In schizophrenia and bipolar mania, quetiapine XR is indicated for doses up to 800 mg/day.

- ***The potential long-term risks associated with quetiapine XR in MDD and GAD are consistent with the known safety profile to date.*** Additional characterization of the potential long-term risks in specific areas has been conducted at the request of the FDA. The characterization included changes in metabolic parameters and tardive dyskinesia, and an additional review was undertaken of risk of sudden cardiac death. No new potential risks were identified in the treatment of MDD and GAD beyond those observed with quetiapine in other indications (schizophrenia and bipolar disorder).

  **With regard to metabolic parameters:**

  – ***Within the MDD/GAD program, where lower daily doses are used (50 to 300 mg/day), the mean changes in metabolic variables appeared generally similar to, or smaller than, those seen in studies in indications using higher doses (up to 800 mg/day).***

  – ***Within the overall clinical study program and the MDD/GAD studies, there was no evidence that quetiapine XR was associated with adverse events potentially related to atherosclerotic cardiovascular disease.*** In addition, no signal was detected in a review of the AERS database.

  – ***Considering all of the available clinical study data, there was no consistent trend for increasing risk of adverse events potentially related to diabetes with quetiapine.*** Within the MDD/GAD studies there was no evidence that quetiapine XR was associated with adverse events potentially related to diabetes. An increased number of adverse events potentially related to diabetes was reported in the long-term randomized withdrawal studies, but not in the placebo-controlled short term studies.

  – ***Evaluation of metabolic data from the MDD and GAD populations did not reveal any metabolic findings or suggest potential long term metabolic risks inconsistent with those seen in the currently approved indications of schizophrenia and bipolar disorder.***

**With regard to tardive dyskinesia:**

- ***While there exists a risk of TD with quetiapine, as indicated in the product labeling, this risk is low, as supported by the frequency of TD AEs associated with quetiapine in clinical studies across all indications (0.2%, 53/26454 patients).*** Results suggest that the risk of TD may be lower in the MDD and GAD populations than in schizophrenia and bipolar patients treated with quetiapine.

**With regard to sudden cardiac death:**

- ***These analyses did not identify a higher risk of sudden cardiac death among patients treated with quetiapine compared to those treated with placebo.***

In terms of overall benefit and risk profile, AstraZeneca considers that

- ***With appropriate labeling and risk management, the benefit risk profile is positive and acceptable in both MDD and GAD.*** Quetiapine XR's benefit and risks have been sufficiently well characterised in a comprehensive clinical development program to appropriately label this unique antidepressant and anxiolytic. With appropriate risk management, quetiapine XR offers patients and prescribers a much needed treatment alternative and a valuable addition to treatment options for both MDD and GAD.

# 1. INTRODUCTION

This document provides information to assist the Advisory Committee in evaluating the benefit-risk profile of quetiapine XR in Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD).

Quetiapine was first developed as an immediate release formulation, which was approved by the FDA in 1997 for the treatment of schizophrenia, and subsequently for bipolar disorder. The extended release formulation, quetiapine XR, was developed to allow once daily administration and faster titration to clinically effective doses. Quetiapine XR, like the immediate release formulation, is approved for schizophrenia, bipolar mania, bipolar depression and bipolar maintenance indications. For these indications, the highest recommended dose is 800 mg/day. AstraZeneca has completed clinical development programs of quetiapine XR in MDD and GAD populations. Separate sNDA filings were made in 2008 seeking approvals in these populations, at a dose range of 50 to 300 mg/day.

The FDA indicated, in the complete response letters on the supplemental NDA for MDD and GAD, that quetiapine XR was efficacious in this indication, but specific long-term safety risks required further examination (metabolic risks and tardive dyskinesia). These risks are included in the current US prescribing information for quetiapine XR. Information on these risks is presented in this document, together with an evaluation of the risk of sudden cardiac death, which was the topic of a recently published article on agents in the same class as quetiapine XR (Ray et al 2009). Data from both the MDD and GAD indications are considered in this document, in order to provide the most comprehensive view of the benefit-risk in these non-psychotic populations and in the dose range used (50 to 300 mg/day).

To assist in the risk characterization and benefit-risk evaluation of quetiapine XR in the MDD and GAD populations, this document includes the following key information:

- ***A proposed mechanism of action of quetiapine XR relevant to MDD and GAD.*** It is important to understand how quetiapine's mechanism of action differs from that of currently approved therapies for MDD and GAD and therefore offers a unique pharmacological profile in these indications.

- ***Information on the indications and unmet medical need for both MDD and GAD.***

- ***A summary of the design and efficacy results of the MDD and GAD programs.*** This information provides context for the benefit-risk assessment.

- ***A general overview of the safety of quetiapine.*** The general safety profile of quetiapine is well characterized, based on extensive clinical investigation in schizophrenia, bipolar disorder, MDD, and GAD. It is estimated that over 22 million patients worldwide have been treated since quetiapine was first approved. A total of 26,454 subjects have been exposed to quetiapine and quetiapine XR in 118 short and long-term clinical studies to date.

- ***Information on specific potential long-term risks,*** as requested by the FDA.

- ***Risk-management and pharmacovigilance activities.*** In these sections, AstraZeneca indicates how risks in the indications of MDD and GAD could be appropriately managed.

- ***Overall benefit-risk evaluation of quetiapine XR.***

## 1.1 Proposed mechanism of action relevant to MDD and GAD

It is important to understand how quetiapine's mechanism of action differs from that of currently approved therapies for MDD and GAD and therefore offers a unique pharmacological profile in these indications.

- ***Quetiapine has activity at dopaminergic, serotonergic and noradrenergic receptors, as demonstrated by converging evidence from preclinical studies and Positron Emission Tomography (PET) studies in man.*** Originally developed as an antipsychotic, quetiapine displays moderate (<60%), transient occupancy of dopamine $D_2$ receptors in the antipsychotic high dose range 400 to 800 mg/day (Mamo et al 2008) and concomitant high 5-$HT_{2A}$ receptor occupancy (Kapur et al 2000). The low $D_2$ receptor occupancy seen even in the higher dose ranges is consistent with the clinically observed low frequency of extrapyramidal side-effects (Farde et al 1992). Moreover, patients treated with quetiapine XR at the antidepressant low dose of 300 mg/day had no more than 26.5% (±8.5%) $D_2$ receptor occupancy (Mamo et al 2008), which is clearly below the levels demonstrated by any antipsychotic treatment.

- ***New mechanistic explanations for the antidepressant and anxiolytic effects seen in clinical studies have been provided by the recently detailed characterization of the human major active metabolite of quetiapine, N-desalkylquetiapine or norquetiapine*** (Jensen et al 2008). Patients treated with quetiapine fumarate have norquetiapine plasma concentrations within the same range as that of quetiapine (Winter et al 2008). Importantly, norquetiapine differs from quetiapine by potently inhibiting the norepinephrine transporter (NET) (Goldstein et al 2008, Jensen et al 2008). The clinical relevance of these findings has been supported by PET demonstration of NET occupancy in subjects treated with representative antidepressant doses (150 to 300 mg/day) of quetiapine XR (Nyberg et al 2008). NET inhibition has not been demonstrated by other atypical antipsychotics at their clinically relevant doses, but is a property shared by well-established antidepressant therapies such as tricyclic antidepressants (eg, imipramine) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, duloxetine and venlafaxine). In addition, norquetiapine displays 5-$HT_{2C}$ receptor antagonism and 5-$HT_{1A}$ partial agonism, and both these mechanisms have been suggested as potential mediators of antidepressant and anxiolytic effects.

- ***In summary, quantitatively important effects in human have been demonstrated by quetiapine at key mechanisms that are well-established targets for antidepressant and anxiolytic treatments.*** Norepinephrine reuptake inhibition has not been demonstrated by other antipsychotics at their clinically relevant doses, but is common to many antidepressants. At antidepressant low doses, quetiapine XR causes considerably less dopaminergic inhibition than that associated with antipsychotic treatments. Taken together, the pharmacological properties of quetiapine have not been described for any other approved drug in MDD or GAD.

- ***Relative to existing drug therapies, quetiapine XR offers physicians and patients a new modality for the treatment of MDD and GAD.***

## 1.2 Prevalence, symptoms, and associated outcomes for MDD

Key facts about Major Depressive Disorder (MDD) are as follows:

- ***Major Depressive Disorder (MDD) is a serious and debilitating illness*** that affects more than 14.8 million American adults in a given year or about 6.7% of the US population aged 18 years and older (National Institutes of Mental Health 2008). Major Depressive Disorder is a chronic and recurrent illness, associated with functional impairment, increased morbidity, and mortality. Its lifetime prevalence is 15 to 20 percent (Kessler et al 2003). According to the World Health Organization, Major Depressive Disorder is currently the 4th leading cause of morbidity in the world, affecting approximately 121 million people worldwide and accounting for nearly 850,000 deaths per year by suicide. By the year 2020, Major Depressive Disorder will be second only to ischemic heart disease as a cause of illness burden worldwide (Murray and Lopez 1997).

- ***MDD is characterized by the presence of a persistently depressed mood or the loss of pleasure for at least 2 weeks.*** Unlike normal bereavement or an occasional episode of "the blues," MDD causes a lengthy period of gloom and hopelessness, and may deprive the sufferer of the ability to take pleasure in activities or relationships that were previously enjoyable. In one study, MDD was associated with substantial symptom severity in over 50% of prevalent cases (Kessler et al 2003). Those suffering from MDD have trouble performing routine social or occupational tasks. Many people with MDD become withdrawn and avoid any type of social activity; many depressed people report a chronic sense of malaise (general discomfort or unease). Relative to the general population, patients with MDD suffer disproportionately from medical illnesses and other psychiatric disorders (Mann 2005).

- ***Patients with severe depressive symptoms may also suffer from psychotic thinking and increased risk for suicide.*** It is estimated that up to 15% of patients with severe depressive symptoms will die by suicide (American Psychiatric Association 2000) and mortality from cardiovascular and respiratory diseases (Ösby 2001).

## 1.3 Unmet medical need in MDD

There remains considerable unmet medical need in MDD.

- ***Many patients still fail to receive optimal treatment despite the availability of a variety of antidepressant medications,*** including multiple compounds representing each of several different proposed mechanisms of action. The general consensus across treatment guidelines is that first-line pharmacotherapy for patients with MDD should consist of either an SSRI or an SNRI. Although both classes of antidepressants are efficacious (Anderson 2000), remission rates are typically less than 50% (Thase ME et al 2001). Approximately 30% of patients treated for MDD with existing antidepressant therapy stop taking their medication during the first month, with over 40% stopping their medication by the end of the third month (Lin et al 1995). This lack of adherence to treatment is in part due to intolerance of the insomnia, agitation, sexual side effects, akathisia, weight loss, nausea and withdrawal symptoms associated with SSRIs and SNRIs. In addition, onset of symptom relief may not occur until after 2-3 weeks of treatment (Rush et al 2003) with only 28% of patients achieving remission within 10-14 weeks (Trivedi 2006). Failing to achieve disease remission severely impairs patient functioning and increases the risk of relapse (McIntyre and O'Donovan 2004). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, after unsuccessful treatment with an SSRI, approximately 25% achieved remission of symptoms after switching to another antidepressant (Rush et al 2006). It is clear that even after multiple treatment cycles, existing therapies fail to achieve remission in a substantial number of patients. The STAR*D authors highlight the need for more broadly effective antidepressant treatments.

- ***In order to address these unmet medical needs, clinicians often switch from one medication to another in the hope of striking the balance between efficacy and tolerability***. Current treatment guidelines recommend that alternative treatments should be considered if a patient experiences problematic adverse events (Table 1 outlines risks associated with different classes of approved pharmacological treatments for MDD and GAD). Likewise if the patient has an inadequate response to antidepressant treatment, the prescriber should consider another antidepressant from the same class or, if two previous medication trials from the same class were ineffective, an antidepressant from a different class (American Psychiatric Association 2000).

- ***Despite the availability of alternative treatment options, there are limitations.*** Due to low disease remission rates achieved using SSRIs and SNRIs, physicians utilize tricyclics (TCAs) and monoamine oxidase inhibitors (MAOIs). However, TCAs are associated with the risk of cardiotoxicity and MAOIs with potentially lethal dietary and drug interactions risks (Hansen et al 2005). Another treatment option is the co-administration of antidepressants such as aripiprazole, an atypical antipsychotic. However, this is the only agent currently approved for the adjunctive

treatment of MDD, and more options are needed to help to increase the proportion of patients who achieve disease remission.

- ***Another area of unmet need in the treatment of MDD stems from the variability of presenting symptoms, which continues to challenge the diagnosis and medical management of MDD.*** One such clinical challenge is differentiating MDD from bipolar depression. Even with widely available screening tools, it is estimated that 35% to 45% of patients with bipolar disorder are initially misdiagnosed with MDD (Hirschfield 2003). This misdiagnosis has implications in the patient's response to treatment as well as outcome and could lead to the possibility of hypomanic or manic switching (Preda et al 2001). Therapies are needed that have the potential to effectively treat both depressive symptoms associated with bipolar disorder, as well as depressive episodes associated with major depressive disorder.

**Table 1 Risks associated with currently approved pharmacological treatments used in MDD and GAD**

| Risk | SSRIs | SNRIs | Tricyclic antidepressants | MAOIs | Other agents |
|---|---|---|---|---|---|
| General side effects | Nausea, diarrhea, anorexia, sexual dysfunction, and stimulatory side effects (agitation, insomnia, and anxiety) (American Psychiatric Association 2000) | Hypertension, sweating (Anderson 2008), lipid elevations (eg, desvenlafaxine). | Cardiotoxicity, high frequency of antimuscarinic effects (eg dry mouth, constipation, blurred vision, urinary disturbances), dizziness, sweating (American Psychiatric Association 2000) | Hypertensive crisis secondary to food or drug interaction, weight gain, serotonin syndrome when taken in close proximity to SSRIs/SNRIs, cardiovascular side effects (hypotension, peripheral edema), sexual dysfunction, and headaches (American Psychiatric Association 2000) | For bupropion, mirtazapine: increased seizures, weight gain, sedation (Anderson 2008),<br>For aripiprazole: EPS and akathisia (Abilify® product label). |
| Long-term risks | Weight gain (Hirschfield 2003)<br>Potential for inducing mania (Preda et al 2001, Ghaemi et al 2000)<br>Sexual dysfunction (Hirschfield 2003, Clayton et al 2002)<br>Extrapyramidal side effects (Lane 1998, Leo 1996)<br>Drug interactions (eg, GI bleeds from combination of SSRIs with NSAIDs (de Abajo and Garcia-Rodriguez 2008, Paton 2005)<br>Neuroleptic malignant syndrome[a] | Potential for inducing mania (Preda et al 2001, Ghaemi et al 2000)<br>Sexual dysfunction (Hirschfield 2003, Clayton et al 2002)<br>Neuroleptic malignant syndrome[a] | Weight gain (Hirschfield 2003)<br>Sexual dysfunction (Hirschfield 2003, Clayton et al 2002)<br>Extrapyramidal side effects (Lane 1998, Leo 1996) | As for side effects | For mirtazapine: Weight gain (Pacher and Kecskemeti 2004)<br>For aripiprazole: Tardive dyskinesia (Abilify® product label) |
| Other | Risk of suicidal behavior/attempts is highest in first few weeks after initiating treatment (Jick 2004, Simon at al 2006).<br>Antidepressant drugs are frequently involved in drug poisoning deaths (Hyman et al 1995, Anderson 2008). Tricyclic antidepressants are especially toxic and have been associated with increased morbidity and mortality in overdose (American Psychiatric Association 2000, Buckley and McManus 2002, Hyman et al 1995). | | | | |

[a] Class labeling for SSRIs and SNRIs.

SSRIs Selective serotonin reuptake inhibitors. SNRIs Serotonin-norepinephrine reuptake inhibitors. MAOIs Monoamine oxidase inhibitors. MDD Major Depressive Disorder. GAD Generalized Anxiety Disorder

## 1.4 Prevalence, symptoms, and associated outcomes for GAD

Key facts about GAD are as follows:

- ***GAD is a debilitating illness*** that affects more than 6.8 million American adults in a given year or about 3.1% of the US population aged 18 years and older (National Institutes of Mental Health 2008).

- ***GAD is characterized by excessive anxiety and worry occurring more days than not for a period of at least 6 months.*** The worry is often associated with feeling restless, keyed up, or on edge. Concentration difficulties, irritability, sleep disturbances, muscle tension, and a variety of somatic symptoms may also be present. The symptoms of GAD are usually chronic in nature, and affect every aspect of the patient's life. GAD reduces work productivity and increases the utilization of health care services, particularly primary care resources. GAD commonly co occurs with other psychiatric disorders, especially MDD. In addition to increased morbidity, GAD is also associated with increased mortality secondary to suicide (Katzman 2009).

- ***Patients with GAD may seek relief from their anxiety symptoms through alcohol or cannabinoids and can develop an iatrogenic substance use disorder.*** Thus the overall socioeconomic burden associated with GAD is significant. It has been estimated that the cost of anxiety disorders in the USA during 1990 was $42 to $47 billion (Wittchen 2002).

## 1.5 Unmet medical need in GAD

Unmet medical needs in GAD include the following:

- ***There are limitations and risks associated with all medications demonstrating efficacy in the treatment of anxiety disorders, including GAD*** (Goodman 2004, see also Table 1). These medications include selective SSRIs, SNRIs, benzodiazepines, buspirone, and tricyclic antidepressants. The general consensus across treatment guidelines is that first-line pharmacotherapy for patients with GAD should consist of either an SSRI or an SNRI. However, these agents have been associated with a relatively slow onset of action, typically 2 to 4 weeks after initiation of treatment (Goodman 2004). In addition, an undesirable effect associated with SSRI or SNRI treatment is sexual dysfunction, which can include symptoms such as decreased libido and erectile dysfunction, leading to treatment nonadherence (Kennedy et al 2001).

- ***Despite the treatment options available, 30% to 40% of patients do not achieve an adequate response from first-line treatment*** (Katzman 2009). Even after an adequate medication treatment trial (sufficient dose and duration), 30% to 60% of

patients continue to exhibit residual symptoms of anxiety (Katzman 2009). Physicians commonly turn to polypharmacy whereby an SSRI or SNRI is used in conjunction with a benzodiazepine and/or sleep aid. Abuse and dependence to benzodiazepines have been well documented, along with the potential for additional drug related adverse effects (Canadian Psychiatric Association 2006).

- ***As discussed for MDD, no single medication will be effective for all patients and many treatment options are needed.*** As a proportion of GAD patients do not tolerate or inadequately respond to currently available treatments, there is a significant need for a new option with a novel mechanism of action and a different tolerability and efficacy profile to those medications currently available.

# 2. DESIGN AND EFFICACY RESULTS OF THE MDD AND GAD PROGRAMS

In the respective Complete Response Letters for MDD and GAD, the FDA stated that the efficacy of quetiapine XR in MDD and GAD has been demonstrated. This section will summarise key design features and efficacy results of the clinical programs with quetiapine XR in MDD and GAD.

Key results included the following:

- ***Quetiapine XR was consistently demonstrated to be efficacious in MDD and GAD.*** Seven out of 8 studies in MDD and all 5 studies in GAD had positive results.

- ***These programs included 6,816 patients dosed with quetiapine XR at doses of 50-300 mg/day.*** Of these patients, 519 were exposed to quetiapine for at least 6 months, and 123 for at least 12 months.

## 2.1 Efficacy in MDD

The efficacy of quetiapine XR in the treatment of Major Depressive Disorder (MDD) was established in:

- 4 placebo-controlled monotherapy clinical studies (Studies 1, 2, 3, and Study 14 in elderly patients). One additional study (Study 4) was a failed study, in which both quetiapine XR and the active comparator (escitalopram) failed to differentiate from placebo.

- 2 placebo-controlled adjunct therapy clinical studies (Studies 6 and 7).

- 1 placebo-controlled monotherapy maintenance (randomized withdrawal) study (Study 5).

All studies included patients who met DSM-IV criteria for Major Depressive Disorder, single or recurrent episodes. Overall, patients were moderately to severely depressed at baseline, which reflects patients seeking medical attention for depression. Details of the studies can be found in Table 2.

## Table 2 Overview of studies in the MDD clinical development program

| Study identifier | Study design and types of control | Test product(s); Dosage regimen [a]; Route of administration | Number of subjects | Duration of treatment | Entry criteria |
|---|---|---|---|---|---|
| Study 1 (Monotherapy, fixed dose) | Multicenter, double-blind, randomized, parallel-group, placebo-controlled; 2-week post-treatment follow-up period | Fixed: QTP 50 mg/day, QTP 150 mg/day, QTP 300 mg/day, or placebo Orally; once a day | 723 randomized; 700 in MITT analysis set (178 50 mg, 168 150 mg, 176 300 mg, 178 placebo) | 6 weeks + 2-week post-treatment follow-up | **Inclusion:** DSM-IV diagnosis of MDD Age 18-65 inclusive HAM-D score .≥22 (Studies 1-4) or ≥20 (Studies 5-7) |
| Study 2 (Monotherapy, fixed dose) | Multicenter, double-blind, randomized, parallel-group, placebo-controlled, active-controlled; 2-week post-treatment follow-up period | Fixed: QTP 150 mg/day, QTP 300 mg/day, duloxetine 60 mg/day, or placebo Orally; once a day | 612 randomized; 587 in MITT analysis set (147 150 mg, 147 300 mg, 141 duloxetine, 152 placebo) | 6 weeks + 2-week post-treatment follow-up | **Exclusion:** Other Axis 1 DSM-IV diagnoses within 6 months of enrollment Unstable medical conditions |
| Study 3 (Monotherapy, flexible dose) | Multicenter, double-blind, randomized, parallel-group, placebo-controlled, 2-week post-treatment follow-up period | Modified fixed (after 14 days): QTP 150 mg/day, QTP 300 mg/day, or placebo Orally; once a day | 310 randomized; 299 in MITT analysis set (147 QTP, 152 placebo) | 8 weeks + 2-week post-treatment follow-up | |
| Study 4 (Monotherapy, flexible dose) | International, multicenter, double-blind, randomized, parallel-group, placebo-controlled, 2-week post-treatment follow-up period | Modified fixed (after 14 days): QTP 150 mg/day, QTP 300 mg/day, escitalopram 10 mg/day, escitalopram 20 mg/day, or placebo Orally; once a day | 471 randomized; 459 in MITT analysis set (154 QTP, escitalopram 152, 153 placebo | 8 weeks + 2-week post-treatment follow-up | |
| Study 5 (Monotherapy maintenance [randomized withdrawal]) | International, multicenter, double-blind, parallel-group, placebo-controlled, randomized withdrawal with open-label run-in and stabilization periods | Flexible: QTP 50 mg /day, QTP 150 mg/day, QTP 300 mg/day, or placebo; Orally; once a day | 1854 began open-label treatment; 787 randomized; 771 in ITT analysis set (387 QTP, 384 placebo) | 4-8 weeks of open-label run-in treatment with QTP; 12-18 weeks of open-label stabilization treatment with QTP; up to 52 weeks of double-blind treatment with QTP or placebo | |

## Table 2 Overview of studies in the MDD clinical development program

| Study identifier | Study design and types of control | Test product(s); Dosage regimen [a]; Route of administration | Number of subjects | Duration of treatment | Entry criteria |
|---|---|---|---|---|---|
| Study 6 (Adjunctive therapy) | Multicenter, double-blind, randomized, parallel-group, placebo-controlled, 2-week post-treatment follow-up period; adjunct (with ongoing antidepressant therapy) | Fixed: QTP 150 mg/day, QTP 300 mg/day, or placebo Orally; once a day | 446 randomized; 432 in MITT analysis set (143 150 mg, 146 300 mg, 143 placebo) | 6 weeks + 2-week post-treatment follow-up | **Inclusion:** as for monotherapy studies, plus: Inadequate response to an approved antidepressant after 6 or more weeks of therapy (HAM-D total score ≥20 and HAM-D item 1 score ≥2) Allowed antidepressants included: including SSRIs (paroxetine, fluoxetine, sertraline, escitalopram, or citalopram), SNRIs, (duloxetine and venlafaxine,) TCA (amitriptyline) and other (bupropion). **Exclusion:** as for monotherapy studies |
| Study 7 (Adjunctive therapy) | Multicenter, double-blind, randomized, parallel-group, placebo-controlled; adjunct (with ongoing antidepressant therapy) | Fixed: QTP 150 mg/day, QTP 300 mg/day, or placebo Orally; once a day | 493 randomized; 418 in MITT analysis set (166 150 mg, 161 300 mg, 160 placebo) | 6 weeks | |
| Study 14 (Monotherapy in elderly patients, flexible dose) | International, multicenter, double-blind, randomized, parallel-group, placebo-controlled; 2-week post-treatment follow-up period. A Short-term treatment in elderly patients | Flexible: QTP 50 mg/day to 300 mg/day, or placebo; Orally once a day | 338 randomized; 335 in MITT analysis set (164 QTP, 171 placebo) | 9 weeks + 2-week post-treatment follow-up | **Inclusion:** as for monotherapy studies, except that patients had to be >65 years old **Exclusion:** as for monotherapy studies, plus MMSE score ≤25 and/or diagnosis of dementia |

[a] Studies 1-7: dosing initiated at 50 mg in evening x 2 days, then 150 mg x 2 days, then 300 mg as appropriate for randomization group assignments; Studies 3-4: dose could be increased to 300 mg after 2 weeks if patients had inadequate response to initial treatment (failure to achieve ≥20% improvement in MADRS total score); Study 5: investigators were to attempt to stabilize the patient at 150 mg then titrate up or down as appropriate; study 14: dosing initiated at 50 mg in evening x 3 days, then increased to 100 mg qd x 3 days, up to 150 mg on day 8; increasing by 50 mg increments up to a maximum of 300 mg by day 22

Patients who had a HAM D-17 score of 20 or greater received quetiapine XR (flexibly dosed at 50 mg, 150 mg, or 300 mg/day) for 4 to 8 weeks. Patients who were stabilized (CGI-S ≤3 and a MADRS total score ≤12) received quetiapine XR for an additional 12 to 18 weeks, within the same dose range. Stability was defined as above with the additional requirement of MADRS total score not to exceed 15 for two consecutive visits and CGI-S not to exceed 5 at any visit.

MMSE Mini Mental State examination

### 2.1.1 Monotherapy

The efficacy of quetiapine XR as monotherapy in the treatment of MDD was demonstrated in two 6-week placebo-controlled, fixed-dose studies (Studies 1 and 2), one 8-week placebo-controlled, flexible-dose study (optional one time dose increase from 150 to 300 mg/day, Study 3) and one 9-week placebo-controlled, flexible-dose study (50 to 300 mg/day) in elderly patients (Study 14, see Table 2). Study 4, in which both quetiapine XR and the active comparator (escitalopram) failed to differentiate from placebo, is not discussed.

The primary endpoint in these studies was change from baseline to end of treatment (Week 6, 8 or 9) in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10 item clinician-rated scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) with total scores ranging from 0 (no depressive features) to 60 (maximum score).

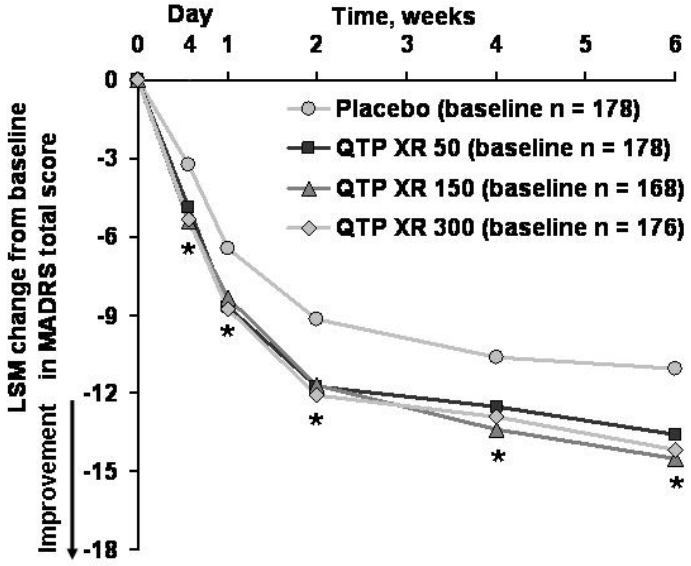
Key findings from these studies were:

- ***Quetiapine XR at doses of 50 mg, 150 mg, and 300 mg/day was superior to placebo in reduction of depressive symptoms as measured by change in MADRS total score and MADRS response rates.*** There was however no clear evidence for greater efficacy at doses above 50 mg/day in Study 1, which was the only short-term study to include the 50 mg dose in a non-elderly population. Figure 1 and Figure 2 show the magnitude of effect and time course of response to quetiapine XR. Study 1, with all three doses, and Study 2, showing quetiapine XR relative to an active comparator (duloxetine), are representative of the findings in the other positive studies.

- ***Statistically significant reductions in depressive symptoms compared to placebo were seen as early as the first time of assessment (Day 4 in Study 1, Week 1 in Study 2).*** See Figure 1 and Figure 2. Continued improvement compared with placebo was demonstrated over the length of the study period.

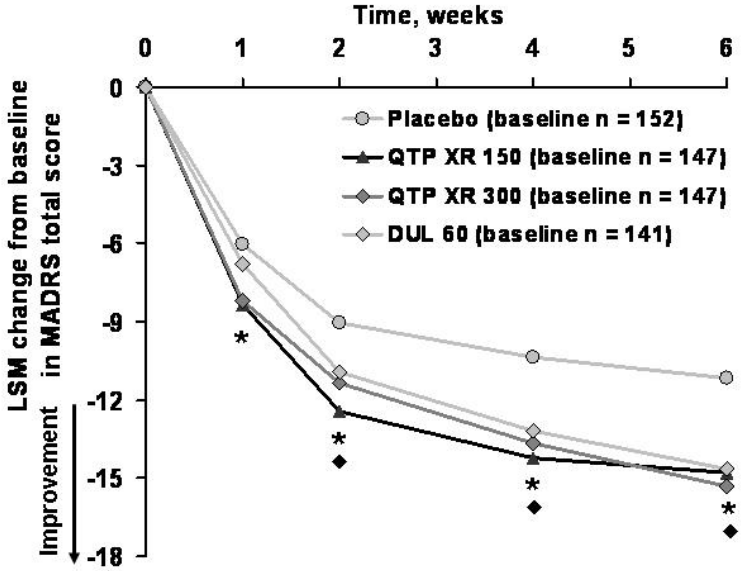
- ***In elderly patients with MDD, quetiapine XR dosed flexibly in the range of 50 to 300 mg/day demonstrated superiority over placebo in reducing depressive symptoms as measured by improvement in MADRS total score and MADRS response rates.*** This study included 166 patients on quetiapine XR and 172 on placebo aged 66 to 89 years, with the proportion of randomized patients over 75 years of age being 19%.

**Figure 1** **Study 1 - MADRS total score change from randomization by visit – LS mean (LOCF, MITT analysis)**




*All QTP XR doses significant at each time point vs placebo ($p < 0.05$)
MITT; LOCF

**Figure 2** **Study 2 - MADRS total score change from randomization by visit – LS mean (LOCF, MITT analysis)**




*All QTP XR doses significant at each time point vs placebo ($p < 0.05$)
◆DUL 60 significant at each time point from week 2 vs placebo ($p < 0.05$)
MITT; LOCF

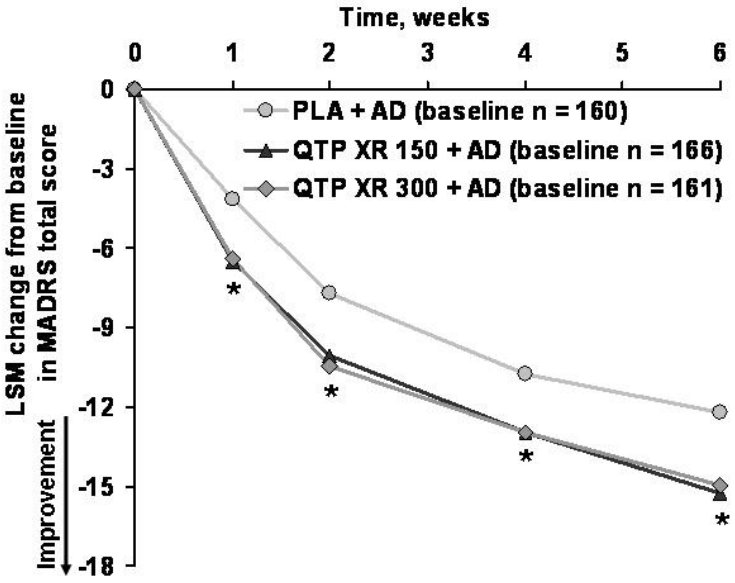
### 2.1.2 Adjunctive therapy

The efficacy of quetiapine XR as adjunct therapy to antidepressants in the treatment of MDD was demonstrated in two 6-week placebo-controlled, fixed-dose studies (Studies 6 and 7, n=936, see Table 2). The primary endpoint for these studies was the change from baseline to end of treatment (Week 6) in the MADRS total score. Quetiapine XR at a dose of 150 mg or 300 mg/day was given as adjunct to existing antidepressant therapy in patients who had previously shown an inadequate response to at least one antidepressant.

The key finding from these studies was that:

- ***Quetiapine XR 300 mg/day as adjunct treatment to other antidepressant therapy was superior to antidepressant alone in reduction of MADRS total score in both studies***, as was the 150 mg dose in one study. Figure 3 demonstrates the magnitude of effect and time course of response to quetiapine XR in Study 7, which is representative of Study 6 also.

**Figure 3** **Study 7 - MADRS total score change from randomization by visit – LS mean (LOCF, MITT analysis)**




*All QTP XR doses significant at each time point vs placebo ($p < 0.05$)
MITT; LOCF

### 2.1.3 Maintenance therapy

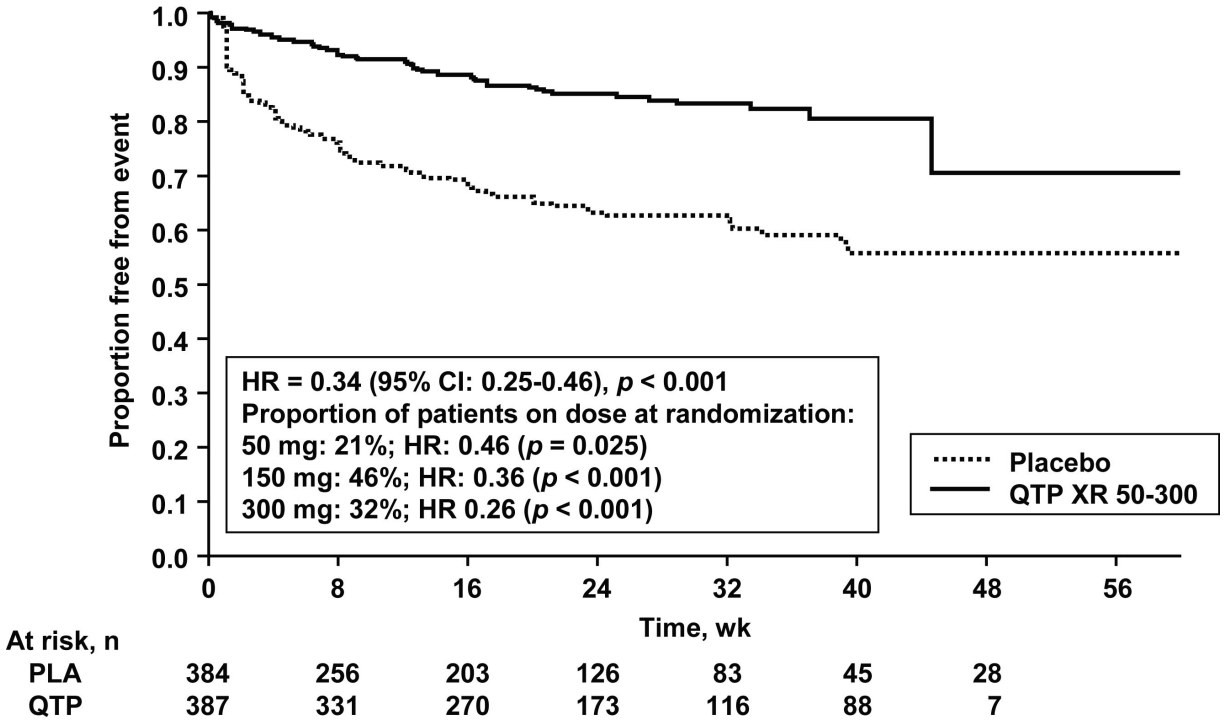
A long-term, maintenance (randomized withdrawal) clinical study consisted of open-label run-in treatment and stabilization phases followed by a double-blind randomized treatment phase.

A total of 1854 patients entered the open-label phase and received quetiapine XR. Patients meeting stabilization criteria (n=771, 42% of the 1854 enrolled patients, see Table 2) were randomized to placebo or to continue on quetiapine XR for up to 52 weeks. Relapse during the double-blind phase was defined as: initiation of other drug treatment by the investigator; additional antidepressant treatment by the patient for at least 1 week; hospitalization; MADRS total score ≥18 at 2 consecutive assessments one week apart or the final assessment if patient discontinued; CGI-S score ≥5; or suicide attempt or imminent risk of suicide.

Key findings from these studies were:

- ***Patients on quetiapine XR experienced a statistically significant longer time to relapse than did patients on placebo (hazard ratio 0.34; p<0.001), representing a 66% relative risk reduction for quetiapine versus placebo.*** This was achieved with patients throughout the dose range; and in a post-hoc analysis, each individual dose (50, 150, 300 mg) of quetiapine XR separated from placebo (hazard ratio 0.46 (p=0.025); 0.36 (p<0.001);0.26 (p<0.001), respectively). As the investigator selected dose based on tolerability and an individual patient's response to therapy, this suggests that there are patients who benefit from higher doses in order to sustain remission. Figure 4 demonstrates the time to relapse in Study 5, shown as the Kaplan-Meier estimates of the proportion of patients without a depressive event over time.

**Figure 4 Time to relapse during double-blind treatment in Study 5 (ITT)**




ITT Intent to treat. QTP Quetiapine.

***Overall conclusions***

In summary, studies with low-dose quetiapine XR 50 to 300 mg/day for MDD demonstrate efficacy when used as fixed dose monotherapy, flexible dose monotherapy, adjunct therapy, and maintenance therapy. In addition to the primary endpoint, secondary endpoints also showed confirmatory evidence of efficacy. Also, across all studies, there was no difference in efficacy across subgroups with respect to gender and age.

## 2.2 Efficacy in GAD

### 2.2.1 Monotherapy

The efficacy of quetiapine XR as monotherapy in the acute treatment of GAD was demonstrated in three 8-week placebo-controlled, fixed dose studies (Studies 9, 10 and 11), and one 9-week placebo-controlled flexible dose study (50 to 300 mg/day) in elderly patients (Study 15), as described in Table 3. (Study 12, the monotherapy maintenance [randomized withdrawal] study, is discussed in Section 2.2.2.)

## Table 3 Overview of studies in the GAD clinical development program

| Study identifier | Study design and types of control | Test product(s); Dosage regimen [a]; Route of admin. | Number of subjects | Duration of treatment | Entry criteria |
|---|---|---|---|---|---|
| Study 9 (Mono-therapy, fixed dose) | Multicenter, double-blind, randomized, parallel-group, placebo-controlled; 2-week post-treatment follow-up period | QTP 50 mg/day, QTP 150 mg/day, QTP 300 mg/day, or placebo; Orally; once a day | 951 randomized; 894 in MITT analysis set (219 50 mg, 226 150 mg, 224 300 mg, 225 placebo) | 8 weeks + 2-week post-treatment follow-up | **Inclusion:** DSM-IV diagnosis of GAD confirmed by MINI, age 18-65 years; HAM-A total score ≥20, MADRS score ≤16. |
| Study 10 (Mono-therapy, fixed dose) | Multicenter, double-blind, randomized, parallel-group, placebo-controlled, active-controlled; 2-week post-treatment follow-up period | QTP 150 mg/day, QTP 300 mg/day, escitalopram 10 mg/day, or placebo; Orally; once a day | 854 randomized; 828 in MITT analysis set (212 150 mg, 201 300 mg, 203 escitalopram, 212 placebo) | 8 weeks + 2-week post-treatment follow-up | **Exclusion:** Other Axis I DSM-IV diagnoses within 6 months of enrollment, or unstable medical condition; |
| Study 11 (Mono-therapy, fixed dose) | International, multicenter, double-blind, randomized, parallel-group, placebo-controlled, active-controlled; 2-week post-treatment follow-up period | QTP 50 mg/day, QTP 150 mg/day, paroxetine 20 mg/day, or placebo; Orally; once a day | 873 randomized; 866 in MITT analysis set (219 50 mg, 216 150 mg, 214 paroxetine, 217 placebo) | 8 weeks + 2-week post-treatment follow-up | |
| Study 12 (Mono-therapy maintenance [randomized withdrawal], flexible dose) | International, multicenter, double-blind, parallel-group, placebo-controlled, randomized withdrawal with open-label run-in and stabilization periods | Flexible: QTP 50 mg /day, QTP 150 mg/day, QTP 300 mg/day, or placebo; Orally; once a day | 1224 began open-label treatment; 432 in ITT analysis set (216 QTP, 216 placebo) [b] | 4-8 weeks of open-label run-in treatment with QTP; 12-18 weeks of open-label stabilization treatment with QTP; up to 52 weeks of double-blind treatment with QTP or placebo | |

## Table 3 Overview of studies in the GAD clinical development program

| Study identifier | Study design and types of control | Test product(s); Dosage regimen [a]; Route of admin. | Number of subjects | Duration of treatment | Entry criteria |
|---|---|---|---|---|---|
| Study 15 (Mono-therapy in elderly patients, flexible dose) | International, multicenter, double-blind, randomized, parallel-group, placebo-controlled; 2-week post-treatment follow-up period. | Flexible: QTP 50 mg/day to 300 mg/day, or placebo; Orally; once a day | 450 randomized; 448 in MITT analysis set (222 QTP, 226 placebo) | 9 weeks + 2-week post-treatment follow-up | **Inclusion:** as for monotherapy studies, except that patients had to be >65 years old; outpatient status at enrolment<br>**Exclusion:** as for monotherapy studies, plus MMSE score ≤25 and/or diagnosis of dementia |

[a] Studies 9-12: dosing initiated at 50 mg in evening x 2 days, then 150 mg x 2 days, then 300 mg as appropriate for randomization group assignments; Study 12: investigators were to attempt to stabilize the patient at 150 mg then titrate up or down as appropriate; Study 15: dosing initiated at 50 mg in evening x 3 days, then increased to 100 mg qd x 3 days, up to 150 mg on Day 8; increasing by 50 mg increments up to a maximum of 300 mg by Day 22

[b] Relapse during the double-blind phase for an anxiety event which was defined as meeting more than one of the following: initiation of other drug treatment for anxiety by the investigator; antianxiety treatment by the patient for at least 1 week; hospitalization for anxiety symptoms; HAM-A total score ≥15 at 2 consecutive assessments one week apart or the final assessment if patient discontinues; CGI-S score ≥5; or a suicide attempt or discontinued from study due to imminent risk of suicide.

GAD Generalized anxiety disorder. MITT Modified intent-to-treat. QTP Quetiapine XR

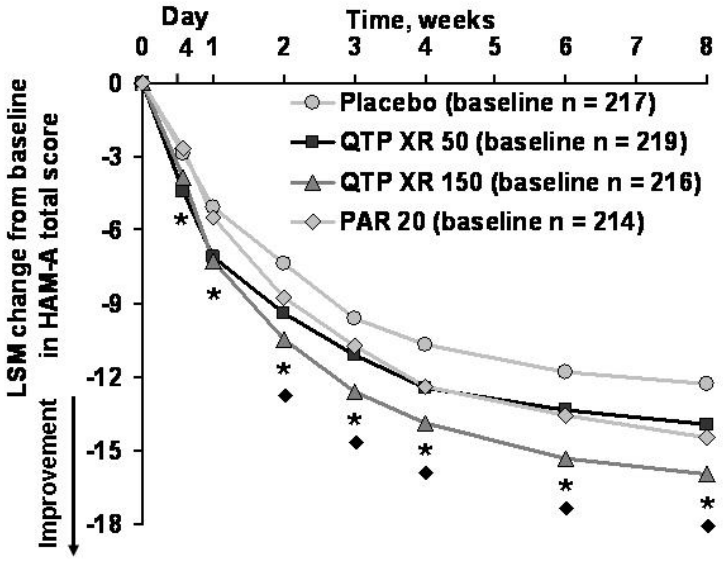
The primary endpoint in these studies was the change from baseline to end of treatment (Week 8 or 9) in the Hamilton Rating Scale for Anxiety (HAM-A), a 14-item clinician-rated scale developed to quantify the severity of anxiety symptomatology total score (anxious mood, tension, fears, insomnia, intellectual impairment, depressed mood, somatic muscular complaints, somatic sensory complaints, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, patient's behavior at interview) with scores ranging from 0 to 56 maximum score. In the non-elderly studies, the mean HAM-A total score at entry was 25.5, and 20.5% of patients scored 29 or greater.Key findings from these studies were:

- ***Quetiapine XR at doses of 50 mg, 150 mg, and 300 mg/day was superior to placebo in reduction of anxiety symptoms as measured by change in HAM-A total score.*** The 300 mg/day dose was shown to be superior to placebo in one of two studies, though the effect size was less than that seen with the lower doses in those studies. Figure 5 demonstrates the magnitude of effect and time course of response to quetiapine XR in Study 11, which included quetiapine XR and an active comparator (paroxetine). This study is generally representative of the findings in the other studies for quetiapine.

- ***Statistically significant improvements were seen as early as the first time of assessment (Days 4 and 8)*** and were also demonstrated at the end of treatment (at Week 8 or 9).

- ***In elderly patients with GAD, quetiapine XR dosed flexibly in the range of 50 to 300 mg/day demonstrated superiority over placebo in reducing anxiety symptoms as measured by improvement in HAM-A total score.***

**Figure 5** **Study 11 - HAM-A total score change from randomization by visit – LS mean (LOCF, MITT analysis)**




*All QTP XR doses significant at each time point vs placebo ($p < 0.05$)
◆PAR 20 significant at each time point from week 2 vs placebo ($p < 0.05$)
MITT; LOCF

### 2.2.2 Maintenance therapy

A long-term, maintenance (randomized withdrawal) clinical study consisted of open-label run-in treatment and stabilization phases followed by a double-blind randomized treatment phase. A total of 1224 patients entered the open-label phase and received flexible doses of quetiapine XR (50 mg, 150 mg, or 300 mg/day) for 4 to 8 weeks. Patients who were stabilized (HAM-A ≤12 and CGI-S ≤ 3) received quetiapine XR for an additional 12 to 18 weeks (average length of stabilization was 15.3 weeks), within the same dose range. Stability was defined as above with the additional requirement of HAM-A total score not to exceed 15 for two consecutive visits and CGI-S not to exceed 5 at any visit.

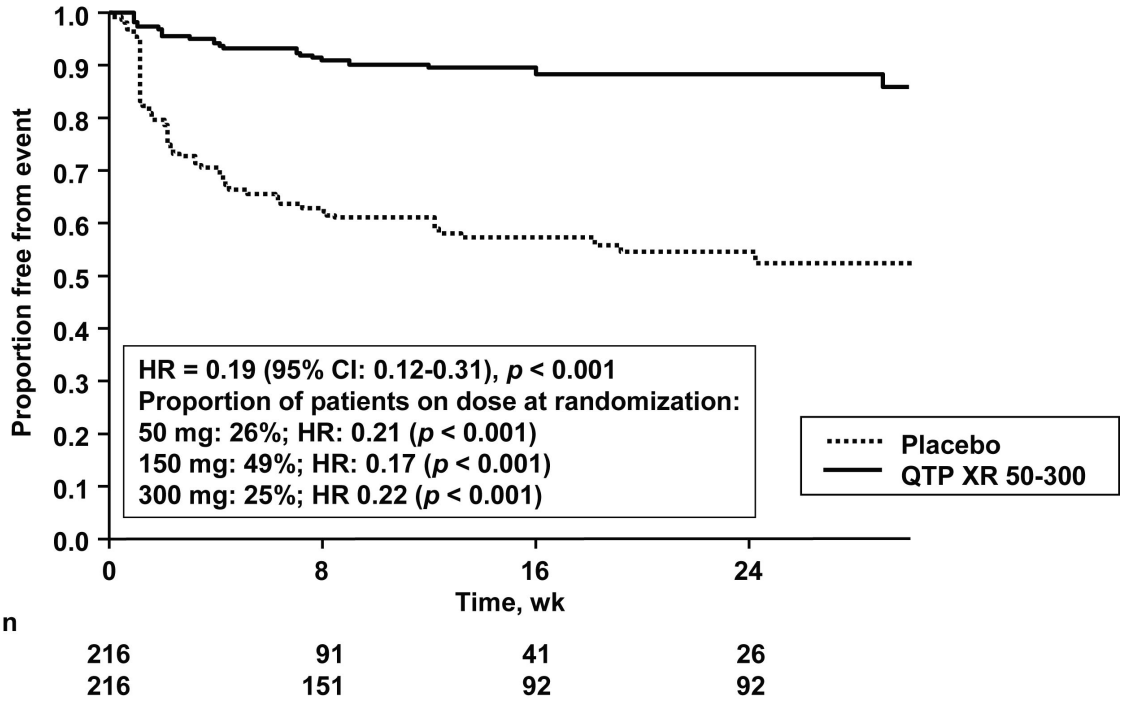
Patients (n=433) meeting these stabilization criteria who in addition had a MADRS score of ≤16 were randomized to placebo or to continue flexibly dosed on quetiapine XR for up to 52 weeks. Relapse during the double-blind phase was defined as: initiation of other drug treatment by the investigator; additional antidepressant treatment by the patient for at least 1 week; hospitalization; HAM-A total score ≥15 at 2 consecutive assessments 1 week apart or the final assessment if the patient discontinued; CGI-S score ≥5; or suicide attempt or imminent risk of suicide.

Key findings from this study were:

- ***Patients receiving quetiapine XR (mean dose 162 mg/day) experienced a statistically significant longer time to relapse than did patients receiving placebo***

***(hazard ratio 0.19, p<0.001), which represents an 81% relative risk reduction for quetiapine vs placebo.*** This was achieved with patients throughout the dose range, and in a post-hoc analysis, each individual dose (50, 150, 300 mg) of quetiapine XR separated from placebo, hazard ratio 0.21 (p<0.001); 0.17 (p<0.001); 0.22 (p<0.001), respectively. As the investigator selected dose based on tolerability and an individual patient's response to therapy, this suggests that there are patients who benefit from higher doses in order to sustain remission. Figure 6 demonstrates the time to relapse in Study 12, shown as the Kaplan-Meier estimates of the proportion of patients without an anxiety event over time.

**Figure 6** **Time to occurrence of an anxiety event in Study 12, Kaplan-Meier curves (ITT analysis set)**




ITT Intent to treat. PLA Placebo. QTP Quetiapine XR.

### *Overall conclusions*

In summary, studies with low-dose quetiapine XR 50 to 300 mg/day for GAD demonstrated efficacy when used as fixed dose monotherapy, flexible dose monotherapy (in elderly patients), and maintenance therapy. In addition to the primary endpoint, secondary endpoints also showed confirmatory evidence of efficacy. Across all studies, there was no difference in efficacy across subgroups with respect to gender and age.

# 3. GENERAL SAFETY OF QUETIAPINE

It is estimated that over 22 million patients worldwide have been treated with quetiapine or quetiapine XR during the 11 years quetiapine has been marketed (see Appendix A4). Approximately 26,000 subjects have been exposed to quetiapine in 118 clinical studies to date. The general safety profile of quetiapine is well characterized, based on extensive clinical study programs investigating the usefulness of quetiapine in the short and long-term treatment of schizophrenia, bipolar disorder, MDD and GAD. Specific clinical studies in elderly patients (>65 years old) with MDD, GAD and dementia-related psychosis have been conducted.

The most common adverse reactions observed in clinical studies that were associated with use of quetiapine XR include: somnolence, dry mouth, hyperlipidemia, constipation, dyspepsia, dizziness, orthostatic hypotension, weight gain, increased appetite, fatigue, hyperglycemia, dysarthria, and nasal congestion.

In relation to the potential long-term risks mentioned in the Complete Response Letter, the existing US prescribing information for quetiapine XR includes warnings on diabetes, weight gain, hyperlipidemia, hyperglycemia and tardive dyskinesia (see Appendix E).

The safety review evaluating quetiapine XR in the treatment of MDD and GAD will briefly summarize the results of the analyses performed for general safety parameters (AEs, laboratory tests, vital signs) and for the specific safety topics (See Section 4), which include metabolic parameters, tardive dyskinesia and sudden cardiac death.

## 3.1 Data sources and pooling

The safety of quetiapine XR in MDD and GAD has been evaluated in 6816 patients who received quetiapine XR, with a total exposure to quetiapine XR of 1405 patient years. Total exposure was higher in the quetiapine XR 150 mg group than in the 50 and 300 mg groups because the 150 mg dose was included in all studies. In the MDD and GAD long-term randomized withdrawal studies, a total of 3079 patients received quetiapine XR, including 519 patients for at least 6 months and 123 patients for at least 12 months.

Safety data for MDD and GAD have been pooled, as these patient populations share a number of similarities. In addition, pooling of data provides more precise estimates of safety effects. Safety data from the short-term monotherapy studies (Studies 1, 2, 3, 4, 9, 10, and 11) are presented in the following section. These data are representative of the types of adverse event seen in the other pools (short-term adjunctive therapy studies in MDD [Studies 6 and 7], elderly studies [Studies 14 and 15], and maintenance (randomized withdrawal) studies [Studies 5 and 12]; see Appendix A).

## 3.2 General safety profile of quetiapine XR in MDD and GAD

No new potential risks were identified in the treatment of MDD and GAD beyond those observed with quetiapine in other indications (schizophrenia and bipolar disorder).

The adverse event profile of quetiapine XR in MDD and GAD is summarised in Table 4 (categories of adverse event) and Table 5 (common adverse events). Key findings are:

- ***Serious adverse events (SAEs):*** In the short-term monotherapy studies, the incidence of SAEs was low and similar in the placebo and the quetiapine XR groups. There was no evident pattern in type of SAEs experienced. The incidence of SAEs appeared to be dose dependent for quetiapine XR within the dose range of 50 to 300 mg/day.

- ***Deaths***: Across all studies, 5 deaths were reported in patients randomized to quetiapine XR and 2 in patients randomized to placebo. For patients randomized to quetiapine XR, 1 death was reported in the short-term monotherapy studies, 1 in the short-term adjunct studies, and 3 in long-term maintenance (randomized withdrawal) studies. Causes of death were homicide, metastatic neoplasm, hypertension and 2 cases reported by the investigator as unknown causes. None of the deaths were considered by the investigator to be related to study drug.

- ***Discontinuations due to AEs:*** In the short-term monotherapy studies, the incidence of discontinuations due to AEs was higher in the quetiapine XR groups compared with the placebo group. Among the quetiapine XR groups, discontinuation due to AEs was lowest in the 50 mg/day group. Sedation and somnolence were the most common reason given for patients discontinuing from quetiapine XR treatment.

- ***Common AEs****:* In the short-term monotherapy studies, the most common AEs were generally reported as mild to moderate in intensity. Events that appeared to be dose dependent included: dry mouth, sedation, somnolence, dizziness, constipation, vision blurred, back pain, vomiting, weight increase, nasal congestion, and disturbance in attention. The type and frequency of AEs reported were consistent with the known safety profile of quetiapine XR in other indications.

- ***Safety in adjunctive therapy:*** Patients treated with quetiapine XR as an adjunct to an antidepressant exhibited generally the same safety observations associated with quetiapine XR monotherapy.

**Table 4 AE incidence in short-term monotherapy studies (Studies 1, 2, 3, 4, 9, 10, and 11)**

| | PLA (N=1313) | ALL QTP (N=2718) | QTP 50 (N=633) | QTP 150 (N=1268) | QTP 300 (N=817) | ESC 10/20 (N=365) | PAR 20 (N=215) | DUL 60 (N=149) |
|---|---|---|---|---|---|---|---|---|
| **Type of adverse event** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| At least one adverse event | 911 (69.4) | 2297 (84.5) | 485 (76.6) | 1091 (86.0) | 721 (88.2) | 304 (83.3) | 156 (72.6) | 131 (87.9) |
| Serious adverse event | 9 (0.7) | 28 (1.0) | 4 (0.6) | 9 (0.7) | 15 (1.8) | 6 (1.6) | 0 (0.0) | 3 (2.0) |
| Adverse event leading to death | 0 | 1 (0.0) | 0 | 1 (0.1) | 0 | 0 | 0 | 0 |
| Drug-related adverse event | 617 (47.0) | 2032 (74.8) | 413 (65.2) | 964 (76.0) | 655 (80.2) | 252 (69.0) | 126 (58.6) | 112 (75.2) |
| Withdrawals due to adverse event | 72 (5.5) | 461 (17.0) | 79 (12.5) | 211 (16.6) | 171 (20.9) | 32 (8.8) | 17 (7.9) | 27 (18.1) |

N Number of patients in treatment group. n Number of patients in the analysis subset. PLA Placebo. QTP Quetiapine XR. ESC Escitalopram. PAR Paroxetine. DUL Duloxetine.
Note: Patients with multiple events in the same category are counted only once in that category.
Note: Percentages are calculated as n/N*100.
Serious: an event that satisfied 1 or more of the following criteria: was fatal, life-threatening, or a congenital abnormality; required or prolonged hospitalization; required medical or surgical intervention to prevent permanent impairment or damage; or resulted in disability or incapacity.
Corresponds to Table SA009a in Module 5.3.5.3 Pooled Safety Data Tables.

**Table 5 Common adverse events (in ≥5% of patients in any treatment group) by decreasing incidence in short-term monotherapy studies (Studies 1, 2, 3, 4, 9, 10, and 11)**

| MedDRA preferred term | PLA (N=1313) n (%) | ALL QTP (N=2718) n (%) | QTP 50 (N=633) n (%) | QTP 150 (N=1268) n (%) | QTP 300 (N=818) n (%) | ESC (N=365) n (%) | PAR (N=215) n (%) | DUL (N=149) n (%) |
|---|---|---|---|---|---|---|---|---|
| Any AE | 705 (53.7) | 2101 (77.3) | 431 (68.1) | 1001 (78.9) | 669 (81.9) | 268 (73.4) | 140 (65.1) | 121 (81.2) |
| Nausea | 123 (9.4) | 301 (11.1) | 50 (7.9) | 155 (12.2) | 96 (11.8) | 99 (27.1) | 48 (22.3) | 56 (37.6) |
| Headache | 234 (17.8) | 373 (13.7) | 83 (13.1) | 194 (15.3) | 96 (11.8) | 103 (28.2) | 45 (20.9) | 32 (21.5) |
| Dizziness | 116 (8.8) | 402 (14.8) | 77 (12.2) | 194 (15.3) | 131 (16.0) | 54 (14.8) | 46 (21.4) | 31 (20.8) |
| Dry mouth | 121 (9.2) | 895 (32.9) | 137 (21.6) | 434 (34.2) | 324 (39.7) | 62 (17.0) | 21 (9.8) | 31 (20.8) |
| Insomnia | 90 (6.9) | 186 (6.8) | 32 (5.1) | 104 (8.2) | 50 (6.1) | 43 (11.8) | 25 (11.6) | 24 (16.1) |
| Sedation | 62 (4.7) | 655 (24.1) | 105 (16.6) | 300 (23.7) | 250 (30.6) | 36 (9.9) | 5 (2.3) | 24 (16.1) |
| Somnolence | 115 (8.8) | 763 (28.1) | 150 (23.7) | 363 (28.6) | 250 (30.6) | 46 (12.6) | 24 (11.2) | 20 (13.4) |
| Diarrhoea | 93 (7.1) | 164 (6.0) | 35 (5.5) | 83 (6.5) | 46 (5.6) | 50 (13.7) | 15 (7.0) | 19 (12.8) |
| Constipation | 44 (3.4) | 208 (7.7) | 34 (5.4) | 93 (7.3) | 81 (9.9) | 27 (7.4) | 8 (3.7) | 17 (11.4) |
| Fatigue | 64 (4.9) | 256 (9.4) | 66 (10.4) | 125 (9.9) | 65 (8.0) | 36 (9.9) | 22 (10.2) | 11 (7.4) |
| Hyperhidrosis | 18 (1.4) | 40 (1.5) | 9 (1.4) | 21 (1.7) | 10 (1.2) | 17 (4.7) | 8 (3.7) | 11 (7.4) |
| Decreased appetite | 23 (1.8) | 54 (2.0) | 10 (1.6) | 24 (1.9) | 20 (2.4) | 18 (4.9) | 3 (1.4) | 8 (5.4) |
| Dyspepsia | 25 (1.9) | 97 (3.6) | 11 (1.7) | 45 (3.5) | 41 (5.0) | 9 (2.5) | 10 (4.7) | 8 (5.4) |
| Pollakiuria | 20 (1.5) | 28 (1.0) | 4 (0.6) | 13 (1.0) | 11 (1.3) | 4 (1.1) | 2 (0.9) | 8 (5.4) |
| Tremor | 19 (1.4) | 40 (1.5) | 9 (1.4) | 17 (1.3) | 14 (1.7) | 8 (2.2) | 11 (5.1) | 8 (5.4) |
| Vomiting | 35 (2.7) | 111 (4.1) | 13 (2.1) | 54 (4.3) | 44 (5.4) | 15 (4.1) | 13 (6.0) | 7 (4.7) |
| Anxiety | 27 (2.1) | 61 (2.2) | 9 (1.4) | 33 (2.6) | 19 (2.3) | 11 (3.0) | 14 (6.5) | 5 (3.4) |
| Increased appetite | 45 (3.4) | 139 (5.1) | 28 (4.4) | 67 (5.3) | 44 (5.4) | 6 (1.6) | 3 (1.4) | 3 (2.0) |
| Nasopharyngitis | 53 (4.0) | 91 (3.3) | 18 (2.8) | 47 (3.7) | 26 (3.2) | 11 (3.0) | 13 (6.0) | 2 (1.3) |

Patients with multiple events falling under the same preferred term are counted only once in that term.
PLA Placebo. QTP Quetiapine XR. ESC Escitalopram. PAR Paroxetine. DUL Duloxetine.
MedDRA Medical Dictionary for Regulatory Affairs, version 10.

Other findings were as follows:

- ***Discontinuation symptoms:*** Patients who had been treated with quetiapine XR monotherapy 50 to 300 mg/day and then abruptly discontinued reported discontinuation symptoms such as insomnia, nausea and vomiting in the first week. Patients treated with quetiapine XR 300 mg/day generally reported more such AEs than those treated with 50 or 150 mg. Patients who were down-titrated from 300 mg to 150 mg/day generally reported fewer discontinuation AEs (nausea excepted) than those abruptly discontinued from treatment at any dose. The aggregate incidence of a patient experiencing one or more of these common discontinuation events one-week post quetiapine XR treatment was 12.1%, compared to 6.7% for placebo.

- ***Suicidality:*** Analysis of suicidality according to the Columbia method (a tool for detecting safety signals regarding increased suicidality compared to placebo) revealed relative risk estimates for quetiapine XR in patients that were not statistically separable from placebo. The incidence of AEs treatment-emergent suicidal ideation or suicide attempt as measured by the Columbia method was low and similar across treatment groups (0.6% for quetiapine XR and 0.5% for placebo).

- ***Agranulocytosis, neutropenia, laboratory data and vital signs:*** The quetiapine IR and XR prescribing information warns that events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including quetiapine. The incidence of agranulocytosis and neutropenia reported for placebo and quetiapine XR treatment groups was low and similar (0.1% for both quetiapine XR and placebo).

  No new findings upon laboratory or vital signs data were found; effects were consistent with the known pharmacological profile of quetiapine XR. Further characterization of metabolic data and QTc data are provided in Sections 4.2 and 4.4.7 respectively.

- ***Extrapyramidal symptoms (EPS) and tardive dyskinesia:*** Incidence of EPS and tardive dyskinesia is further characterized in Section 4.3.

- ***Changes in sexual function:*** A non-inferiority analysis of the CSFQ (Changes in Sexual Function Questionnaire) total score across the short-term MDD and GAD studies demonstrated quetiapine XR to be non-inferior to placebo in both males and females. The 95% CI for the difference in mean CSFQ total score between quetiapine XR and placebo was -0.36 to 0.59 and was above the prespecified non-inferiority limit of -0.75.

- ***Long-term safety:*** Patients treated with quetiapine XR during the open-label treatment phase (up to 26 weeks) of the maintenance (randomized withdrawal) studies (Study 5 and 12) exhibited generally the same safety observations associated with quetiapine XR administration as did the patients in the short-term studies,

regardless of whether they continued into the randomized treatment phase. Patients generally reported few adverse events after 16 to 26 weeks of open-label treatment. In the randomized phase the only event with a frequency greater than 5% and more common in the quetiapine XR group compared with placebo was weight increase.

# 4. SPECIFIC SAFETY TOPICS

This section addresses the topics specifically identified in the FDA's complete response letter on the MDD submission (metabolic risk and tardive dyskinesia; see Section 1 above). In addition, AstraZeneca has agreed with FDA to present information on the risk of sudden cardiac death with quetiapine, following publication of a recent paper by Ray et al 2009 describing a potential linkage between this risk and the use of typical antipsychotics.

## 4.1 Data sources and pooling

In this section, safety data have been pooled across different study types to allow a more comprehensive review of the specific topics. These included AstraZeneca-sponsored studies that had completed as of December 31, 2008. The safety pools are:

**Pool A**

***All studies:*** This pool contains data from all clinical studies conducted by AstraZeneca involving quetiapine IR or quetiapine XR, regardless of indication. This pool comprises 118 studies involving 26454 patients treated with quetiapine XR with a total exposure of 7890 patient years. The total exposure to quetiapine by indication in patient years is 3120 (schizophrenia), 2937 (bipolar disorder), 1405 (MDD and GAD), and 428 (all other patient populations).

**Pool B**

***Placebo-controlled short-term studies:*** This pool contains data from all short term (up to 12 weeks treatment duration) clinical studies conducted by AstraZeneca involving quetiapine IR and XR that included a placebo control arm, regardless of indication. This pool comprises 35 studies involving 13212 patients (8853 on quetiapine and 4359 on placebo) with a total exposure of 982 patient years on quetiapine.

**Pool C**

***All long-term randomized withdrawal studies:*** This pool contains data from 8 long-term randomized withdrawal clinical studies conducted by AstraZeneca involving quetiapine IR and XR regardless of indication. This pool comprises 2043 patients on quetiapine and 2016 on placebo during randomized treatment, with a total exposure of 1026 patient years on quetiapine.

**Pool D**

***All MDD and GAD studies:*** This pool contains data from all clinical studies conducted by AstraZeneca involving quetiapine XR for the treatment of MDD or GAD. This pool comprises 13 studies involving 6,816 patients with a total exposure of 1404.8 patient years on quetiapine.

**Pool E**

***Long-term MDD and GAD randomized withdrawal studies:*** This pool contains data from long-term randomized withdrawal studies in patients with MDD (Study 5) or GAD (Study 12). This pool comprises 607 patients on quetiapine and 601 on placebo during randomized treatment, with a total exposure of 242 patient years on quetiapine.

Pediatric and elderly patients are included in both Pool A and Pool B.

## 4.2 Metabolic variables

In the current labeled indications of schizophrenia and bipolar disorder, quetiapine XR has warnings regarding hyperglycemia and diabetes mellitus, hyperlipidemia, and weight gain (see Appendix E for current label text). The question before this Advisory Committee is the extent to which these risks are present, and whether they are manageable with appropriate labeling and risk management, in a population of patients with MDD or GAD.

Throughout this section, AstraZeneca presents data for weight, blood glucose, and lipids (total cholesterol, HDL, LDL, and triglycerides). This briefing document however is part of a broader series of efforts by AstraZeneca to assess these metabolic variables. Another effort to assess these variables forms part of a submission to FDA by AstraZeneca in June 2008 in response to a January 8, 2008, Division of Psychiatry Products request to the manufacturers of the atypical antipsychotic drugs for detailed summaries of data on changes in metabolic parameters. Certain data pertaining to changes in weight during long-term treatment with quetiapine have been published (Brecher et al 2007). More recently a poster including a representation of changes in metabolic parameters has been presented (Newcomer et al 2009). The methodology used in the presentation of the data in the poster is different but is complementary to those that follow in this document. Further, the analysis underlying the poster is being further developed as a part of the ongoing review of evolving data to more comprehensively characterize changes in metabolic variables observed following short- and longer-term treatment with quetiapine across a range of psychiatric diagnoses.

Throughout this section, AstraZeneca presents laboratory data for weight, blood glucose, and lipids (total cholesterol, HDL, LDL, and triglycerides) from:

- Pool A: All studies
- Pool E: Long-term MDD and GAD randomized withdrawal studies

Other sources of information also summarized include

- Adverse event data for events potentially related to diabetes mellitus and for events potentially related to atherosclerotic cardiovascular disease. The sources for these adverse events include:
  - Pool A: All studies
  - Pool B: Placebo-controlled short-term studies
  - Pool C: All long-term randomized withdrawal studies
  - Pool E: Long-term MDD and GAD randomized withdrawal studies
- A controlled, 6-month study of glucose tolerance in patients with schizophrenia

### 4.2.1 Approach to exploration of long-term metabolic laboratory data

Blood samples for the measurement of blood glucose, LDL, and triglycerides should be taken in a fasting status to be reliable. In study protocols with quetiapine, patients were instructed not eat or drink fluids, other than water, from midnight the night before until after sample collection the following morning. The samples were collected after a minimum 8-hour fast the night before the scheduled study visit. The date and time of sample collection and the time that the patient last ate were recorded. In the randomized phase of the longer-term MDD and GAD studies, 89% of glucose samples were confirmed as being drawn in the fasted state. This does not completely exclude the possibility of caloric intake before sampling.

Fasting blood samples were however not obtained in all of AstraZeneca's clinical studies with quetiapine. The interpretative value of the non-fasting lab values for blood glucose, LDL, and triglycerides is limited. In this section only data from fasting samples for these variables will therefore be presented, since this is the most relevant data.

Metabolic variables are summarized in two ways. First mean changes from a baseline value through time windows are displayed. As well proportions of patients with a clinically relevant shift during treatment are also displayed.

Potentially clinically relevant shifts and values during treatment for each metabolic variable are defined as:

- Weight $\geq$ 7% increase from baseline
- Glucose $\geq$ 126 mg/dL
- Total cholesterol $\geq$ 240 mg/dL
- HDL $\leq$ 40 mg/dL
- LDL $\geq$ 160 mg/dL

- Triglycerides ≥ 200 mg/dL

These shift thresholds and time windows were also employed as part of the submission to FDA by AstraZeneca in support of the January 8, 2008, Division of Psychiatry Products request for summaries of data to evaluate the effects of atypical antipsychotic drugs on metabolic parameters.

The data displayed for each metabolic variable were generated as an attempt to address clinical questions summarized in Table 6.

## Table 6 Key questions and data sources for metabolic risks

| Questions | Data source and methodology | Data presentation |
|---|---|---|
| **Across all indications** | | |
| Are there longer-term changes in the MDD and GAD populations and how do the changes compare with those changes observed in other uses of quetiapine? | This addresses whether outcomes associated with higher doses, as used in the clinical settings of schizophrenia and bipolar disorder, are quantitatively different from changes seen with the lower doses used in the development program for MDD and GAD.<br>This question is addressed using 2 cohorts of patients from Pool A for each clinical setting; those receiving 24 weeks and 48 weeks of quetiapine therapy for glucose and weight.<br>For lipid variables the cohorts were based on those receiving at least 12 and at least 24 weeks of therapy. | For each clinical setting, summary statistics (n, mean, SD) for each metabolic variable include the baseline value, the change from baseline value, as well as dose information. No formal statistical analyses were performed across indications, as data were collected in distinct clinical programs for each separate indication.<br>Tables using this approach: Table 7, Table 10, Table 13, Table 16, Table 19, and Table 22. |
| **Across MDD and GAD studies** | | |
| Are there differences in mean changes between quetiapine XR and placebo?<br>Are there differences in the proportions of patients having a potentially clinically significant change between quetiapine XR and placebo?<br>Are there differences among doses in the range of 50 to 300 mg/day? | These questions are addressed using the data from the pooled long term MDD and GAD randomized withdrawal studies (Pool E). Both study designs allowed for up to 26 weeks of open-label therapy (50 to 300 mg/day) prior to the randomized period. At randomization, patients either continued on quetiapine XR or were withdrawn from quetiapine XR. The OL baseline value was used to calculate change over time because it represents the initiation of quetiapine XR therapy in all patients in these studies. The design of these studies allows for comparisons of the long-term effects of continuing quetiapine XR treatment versus withdrawal of quetiapine XR treatment. Also, the studies employed a flexible dose design, where investigators were instructed to optimize individual patient treatment.<br>Dose groups were formed, post-hoc, based on the median daily dose of quetiapine XR received in an attempt to explore the potential for long-term effects of quetiapine XR being related to dose. It is important to note each study was designed to stop after a pre-specified number of events, so the fall in patient numbers between assessments is in part a function of the design. | 1. Mean change for patients during the open-label portion<br>2. Mean change for patients during the open-label portion that were randomized to placebo or to continue on quetiapine XR. These summaries are presented for weeks 12, 24, 36 and 48 of the randomized phase.<br>3. Mean changes as directly above for each of the post-hoc dose groups.<br>4. Proportions of patients with a potentially clinically significant change or value from OL baseline for placebo, quetiapine XR and post-hoc dose groups.<br>No formal statistical analyses were performed, as the evaluations are made from the start of open-label, rather than the point of randomisation. In addition, dose |

**Table 6 Key questions and data sources for metabolic risks**

| Questions | Data source and methodology | Data presentation |
|---|---|---|
| | | cohorts were defined post-hoc, using doses observed during the study.<br>Tables using this approach: Table 8, Table 11, Table 14, Table 17, Table 20, Table 23. |
| What are the changes observed continuing quetiapine XR after 12-26 weeks of exposure to quetiapine XR? | This question is addressed in four cohorts of patients from Pool E; those randomized and receiving quetiapine XR for an additional 12, 24, 36 and 48 weeks. | For each cohort, summary statistics (n, mean, SD) for each metabolic variable include the randomized baseline value (represents the change from open label baseline) and the change from the open-label baseline value.<br>Tables using this approach: Table 9, Table 12, Table 15, Table 18, Table 21, Table 24. |
| What are the changes observed after 12-26 weeks of exposure to quetiapine XR when quetiapine XR is withdrawn? | This question is addressed in four cohorts of patients from Pool E; those randomized and receiving placebo for 12, 24, 36 and 48 weeks. | |

n number of patients, SD standard deviation, GAD Generalized Anxiety Disorder, MDD Major Depressive Disorder

The following sections present the metabolic data.

### 4.2.2 Weight

This section presents data on changes in body weight observed with quetiapine treatment; the approach is described in Section 4.2.1 above.

Across indications—without a comparison to placebo

- Weight increases were observed across the quetiapine clinical study program.
- Across indications, weight gain observed after approximately one year of treatment with quetiapine appeared to be lower in MDD and GAD than in the indications of schizophrenia and bipolar disorder, where higher doses are used (Table 7).

Across MDD and GAD

- 48 weeks after randomization in the randomized withdrawal studies, mean changes in weight were higher on quetiapine XR than on placebo (Table 8). The mean change over the open-label phase with quetiapine XR appeared to be dose related (Table 8). However, the rate of change for weight appeared to be slower for the low-dose group (<100mg). For quetiapine XR, the percentages of patients with at least a 7% increase in weight appear to be dose related (Table 8).
- After withdrawing quetiapine XR and randomization to placebo, mean weight decreased towards levels observed at the start of open label (Table 9).
- Of the overall 2.7 kg mean weight increase with quetiapine XR the majority of the weight increase was seen during the open label treatment. During the randomized period the additional mean weight increase was <1.0 kg (Table 9).

**Table 7 Weight (kg) changes in patients from Pool A (all studies) with at least 24 weeks of quetiapine exposure, by indication**

| | | Monotherapy | | | | | | | | Adjunct therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | | Schizophrenia | | Bipolar disorder monotherapy | | MDD+GAD (pooled) | | Monotherapy Total | | Bipolar disorder (adjunct to lithium or valproate) | |
| 24 | n[a] | 733 | | 639 | | 235 | | 1659 | | 1093 | |
| | Baseline mean (SD) | 74.1 | (17.0) | 71.8 | (17.6) | 79.3 | (19.8) | 74.1 | (17.7) | 85.2 | (20.8) |
| | Mean change (SD) | 2.5 | (6.7) | 2.5 | (4.8) | 1.2 | (4.0) | 2.2 | (5.6) | 4.4 | (6.5) |
| | Modal dose (SD) | 510.2 | (208.6) | 551.8 | (184.6) | 187.7 | (93.6) | 478.2 | (224.4) | 505.6 | (141.3) |
| 48 | n[a] | 209 | | 85 | | 73 | | 383 | | 123 | |
| | Baseline mean (SD) | 72.3 | (17.4) | 73.1 | (15.7) | 82.5 | (20.3) | 75.1 | (18.0) | 87.3 | (22.1) |
| | Mean change (SD) | 4.3 | (8.9) | 2.6 | (5.3) | 1.8 | (6.2) | 3.1 | (7.9) | 5.8 | (9.8) |
| | Modal dose (SD) | 475.6 | (208.3) | 483.5 | (171.7) | 172.6 | (101.1) | 427.1 | (221.6) | 485.4 | (126.5) |

[a] Number of patients with an assessment at baseline and at least one assessment post baseline.
GAD Generalized anxiety disorder; MDD Major depressive disorder; n Number of patients in category; SD Standard deviation

**Table 8 Weight (kg) change from open-label baseline in Pool E (long-term MDD and GAD randomized withdrawal studies)**

| Treatment and dose | | Up to 26 weeks Open-label stabilization (all patients receiving QTP XR) | | Randomized withdrawal phase, observed case change from OL baseline | | | | | Patients with potentially clinically significant change from OL baseline, n/N (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OL Baseline | Change at end of OL (LOCF) | Randomized Baseline | Week 12 | Week 24 | Week 36 | Week 48 | Percentage change | At randomized baseline | At randomized final |
| Placebo | n | | | 596 | 551 | 195 | 90 | 35 | ≥7% increase | 71/596 (11.9) | 55/552 (10.0) |
| | Mean | | | 1.4 | 0.6 | 0.1 | -0.0 | 0.3 | ≥7% decrease | 19/596 (3.2) | 28/552 (5.1) |
| | SD | | | 4.1 | 5.2 | 5.6 | 6.3 | 4.4 | | | |
| Quetiapine XR ≤100 mg/day | n | | | 146 | 140 | 66 | 34 | 15 | ≥7% increase | 4/147 (2.7) | 11/140 (7.9) |
| | Mean | | | 0.6 | 0.6 | 0.7 | 1.9 | 2.1 | ≥7% decrease | 1/147 (0.7) | 3/140 (2.1) |
| | SD | | | 2.5 | 3.1 | 3.0 | 3.2 | 3.3 | | | |
| Quetiapine XR >100 mg/day to ≤200 mg/day | n | | | 278 | 260 | 115 | 56 | 23 | ≥7% increase | 39/280 (13.9) | 43/264 (16.3) |
| | Mean | | | 2.1 | 1.5 | 2.1 | 2.7 | 3.2 | ≥7% decrease | 7/280 (2.5) | 11/264 (4.2) |
| | SD | | | 4.7 | 4.9 | 5.3 | 5.9 | 7.2 | | | |
| Quetiapine XR >200 mg/day to ≤300 mg/day | n | | | 180 | 172 | 92 | 54 | 21 | ≥7% increase | 34/180 (18.9) | 47/173 (27.2) |
| | Mean | | | 2.7 | 2.9 | 3.1 | 3.0 | 2.6 | ≥7% decrease | 4/180 (2.2) | 6/173 (3.5) |
| | SD | | | 5.5 | 5.1 | 5.8 | 6.0 | 6.2 | | | |
| Quetiapine XR Total | n | 3070 | 1939 | 604 | 572 | 273 | 144 | 59 | ≥7% increase | 77/607 (12.7) | 101/577 (17.5) |
| | Mean | 81.3 | 1.5 | 1.9 | 1.7 | 2.1 | 2.6 | 2.7 | ≥7% decrease | 12/607 (2.0) | 20/577 (3.47) |
| | SD | 21.6 | 4.2 | 4.6 | 4.7 | 5.1 | 5.4 | 6.0 | | | |

GAD Generalized anxiety disorder; LOCF Last observation carried forward; MDD Major depressive disorder; N Total number of patients in treatment group; n Number of patients in category; OL Open-label; QTP XR Quetiapine extended-release; SD Standard deviation
Proportion of patients with potentially clinically significant change is not adjusted for the longer exposure in the quetiapine XR treatment group

**Table 9 Weight (kg) change from open-label baseline in study completion cohorts from Pool E (long term MDD and GAD randomized withdrawal studies)**

| | | Week of Randomised Phase | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Week 0 (Randomisation) | | | Week 12 | | | Week 24 | | | Week 36 | | | Week 48 | | |
| | Completer Cohort | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **Placebo** | Week 48 Cohort | 35 | 0.4 | 3.1 | 35 | 0.2 | 4.0 | 35 | -0.5 | 4.4 | 34 | 0.8 | 4.7 | 35 | 0.3 | 4.4 |
| | Week 36 Cohort | 90 | 0.8 | 4.7 | 90 | -0.1 | 6.1 | 90 | -0.4 | 6.2 | 90 | 0.0 | 6.3 | - | - | - |
| | Week 24 Cohort | 195 | 1.3 | 4.6 | 194 | 0.6 | 5.5 | 195 | 0.1 | 5.6 | - | - | - | - | - | - |
| | Week 12 Cohort | 551 | 1.4 | 4.1 | 551 | 0.6 | 5.2 | - | - | - | - | - | - | - | - | - |
| **Quetiapine XR** | Week 48 Cohort | 58 | 2.4 | 3.7 | 59 | 1.9 | 6.3 | 58 | 3.1 | 5.1 | 59 | 3.3 | 5.7 | 59 | 2.7 | 6.0 |
| | Week 36 Cohort | 143 | 1.8 | 3.5 | 142 | 2.1 | 5.0 | 143 | 2.5 | 4.8 | 144 | 2.6 | 5.4 | - | - | - |
| | Week 24 Cohort | 273 | 1.7 | 3.5 | 270 | 2.1 | 4.6 | 273 | 2.1 | 5.1 | - | - | - | - | - | - |
| | Week 12 Cohort | 570 | 1.9 | 4.5 | 572 | 1.7 | 4.7 | - | - | - | - | - | - | - | - | - |

n number of patients, SD standard deviation

### 4.2.3 Blood glucose (fasting)

This section presents data on changes in fasting glucose observed with quetiapine treatment. The patient groups and data approaches were the same as those described in Section 4.2.1 above.

Across indications—without comparison to placebo

- Fasting glucose increases were observed across the quetiapine clinical study program. Mean fasting glucose increase was less than approximately 5% across all indications at 48 weeks.

- Across indications, glucose increases observed after approximately one year of treatment with quetiapine appeared to be similar in MDD and GAD and the indications of schizophrenia and bipolar disorder, where higher doses are used (Table 10).

Across MDD and GAD

- Over the 48-week period following randomization, in the randomized withdrawal studies, the mean increases in fasting glucose were variable and similar between quetiapine XR and placebo (Table 11). There was no apparent relationship to dose for mean changes in fasting glucose nor was there any obvious trend toward larger increases in fasting glucose over time with quetiapine XR (Table 11). The proportion of patients with potentially clinically significant values of glucose (≥126 mg/dL) was generally low, but appeared higher for quetiapine XR than placebo (3.9% vs. 2.5%, Table 11) over the 48-week post randomization period.

- Relative to mean fasting glucose levels reached at the end of the open label phase, subsequent mean fasting glucose changes appeared similar in patients whether randomized to continue with quetiapine XR or withdraw from quetiapine XR treatment. Mean fasting glucose values did not appear to continue increasing in the longer term (Table 12).

Because of the conflicting information on the prevalence and extent of hyperglycemia, diabetes mellitus and weight gain after atypical antipsychotic treatment, AstraZeneca conducted a clinical study (Study 125) to assess the differential effects of quetiapine, olanzapine, and risperidone from over 24 weeks on glucose metabolism, lipid levels, and weight-related parameters in patients with schizophrenia. A summary of Study 125 is in Section 4.2.9. No statistically significant change was seen with quetiapine for the primary endpoint, change from randomization in 2-hour AUC of plasma glucose following an oral glucose tolerance test after 24 weeks of treatment (Table 27).

**Table 10 Glucose (fasting, in mg/dL) changes in patients from Pool A (all studies) with at least 24 weeks of quetiapine exposure, by indication**

| | | Monotherapy | | | | | | | | Adjunct therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | | Schizophrenia | | Bipolar disorder monotherapy | | MDD+GAD (pooled) | | Monotherapy Total | | Bipolar disorder (adjunct to lithium or valproate) | |
| 24 | n[a] | 148 | | 518 | | 123 | | 789 | | 374 | |
| | Baseline mean (SD) | 91.4 | (11.7) | 92.8 | (15.4) | 93.3 | (14.6) | 92.6 | (14.7) | 91.0 | (15.1) |
| | Mean change (SD) | 4.5 | (20.2) | 3.8 | (21.4) | 3.1 | (23.6) | 3.8 | (21.5) | 4.8 | (21.1) |
| | Modal dose (SD) | 623.8 | (144.0) | 526.3 | 182.6 | 181.3 | (88.8) | 490.6 | (214.7) | 514.6 | (147.3) |
| 48 | n[a] | 5 | | 140 | | 56 | | 201 | | 74 | |
| | Baseline mean (SD) | 105.8 | (14.3) | 93.5 | (13.0) | 90.8 | (13.3) | 93.1 | (13.3) | 92.9 | (20.9) |
| | Mean change (SD) | -7.6 | (15.0) | 5.7 | (17.2) | 4.0 | (16.2) | 4.9 | (16.9) | 2.6 | (14.2) |
| | Modal dose (SD) | 640.0 | (167.3) | 475.0 | (166.3) | 181.3 | (100.7) | 397.3 | (203.3) | 478.4 | (130.6) |

[a] Number of patients with an assessment at baseline and at least one assessment post baseline.
GAD Generalized anxiety disorder; MDD Major depressive disorder; n Number of patients in category; SD Standard deviation

**Table 11 Glucose (fasting, in mg/dL) change from open-label baseline in baseline in Pool E (long term MDD and GAD randomized withdrawal studies)**

| Treatment and dose | | Open-label stabilization (all patients receiving QTP XR) | | Randomized withdrawal phase, observed case change from OL baseline | | | | | Patients with potentially clinically significant value (≥126 mg/dL), from OL baseline, n/N (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OL baseline | End of OL | Randomized baseline | Week 12 | Week 24 | Week 36 | Week 48 | At randomized baseline/at end of OL (Patients 'normal' at start of OL) | At randomized final |
| Placebo | n | | | 491 | 398 | 159 | 73 | 27 | | |
| | Mean | | | 2.68 | 4.22 | 6.82 | 6.90 | 5.07 | 16/487 (3.3%) | 10/397 (2.5%) |
| | SD | | | 16.85 | 15.77 | 17.69 | 21.68 | 30.78 | | |
| Quetiapine XR ≤100 mg/day | n | | | 107 | 109 | 50 | 28 | 12 | | |
| | Mean | | | -0.89 | 5.19 | 6.34 | 6.64 | 5.67 | 1/107 (0.9%) | 2/106 (1.9%) |
| | SD | | | 9.91 | 15.57 | 20.30 | 12.94 | 9.37 | | |
| Quetiapine XR >100 mg/day to ≤200 mg/day | n | | | 227 | 204 | 88 | 40 | 15 | | |
| | Mean | | | 3.38 | 5.46 | 7.14 | 6.48 | 6.87 | 6/227 (2.6%) | 9/200 (4.5%) |
| | SD | | | 16.96 | 20.79 | 21.35 | 17.88 | 8.25 | | |
| Quetiapine XR >200 mg/day to ≤300 mg/day | n | | | 147 | 129 | 72 | 41 | 15 | | |
| | Mean | | | 2.11 | 4.99 | 7.15 | 4.39 | 1.67 | 0/143 (0.0%) | 6/126 (4.8%) |
| | SD | | | 11.99 | 15.11 | 13.76 | 18.75 | 11.15 | | |
| Quetiapine XR total | n | 2825 | 1475 | 481 | 442 | 210 | 109 | 42 | | |
| | Mean | 91.5 | 2.22 | 2.04 | 5.26 | 6.95 | 5.73 | 4.67 | 7/477 (1.5%) | 17/432 (3.9%) |
| | SD | 13.4 | 14.50 | 14.27 | 18.02 | 18.73 | 16.99 | 9.72 | | |

GAD Generalized anxiety disorder; LOCF Last observation carried forward; MDD Major depressive disorder; N Total number of patients in treatment group; n Number of patients in category; OL Open-label; QTP XR Quetiapine extended-release; SD Standard deviation
Proportion of patients with potentially clinically significant value is not adjusted for the longer exposure in the quetiapine XR treatment group

**Table 12** **Glucose (fasting, in mg/dL) change from open-label baseline in study completion cohorts from Pool E (long term MDD and GAD randomized withdrawal studies)**

| | | Week of Randomised Phase | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Week 0 (Randomisation) | | | Week 12 | | | Week 24 | | | Week 36 | | | Week 48 | | |
| | Completer Cohort | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **Placebo** | Week 48 Cohort | 26 | -0.38 | 38.37 | 24 | 6.83 | 31.84 | 23 | -1.00 | 27.41 | 25 | 1.68 | 31.02 | 27 | 5.07 | 30.78 |
| | Week 36 Cohort | 68 | 4.68 | 27.14 | 67 | 8.06 | 22.02 | 66 | 6.38 | 21.62 | 73 | 6.90 | 21.68 | - | - | - |
| | Week 24 Cohort | 145 | 5.69 | 22.53 | 142 | 7.61 | 18.54 | 159 | 6.82 | 17.69 | - | - | - | - | - | - |
| | Week 12 Cohort | 372 | 2.39 | 17.15 | 398 | 4.22 | 15.77 | - | - | - | - | - | - | - | - | - |
| **Quetiapine XR** | Week 48 Cohort | 38 | 1.11 | 15.88 | 39 | 7.21 | 19.39 | 38 | 9.58 | 14.65 | 38 | 7.11 | 9.89 | 42 | 4.67 | 9.72 |
| | Week 36 Cohort | 95 | 2.05 | 12.92 | 99 | 5.65 | 16.21 | 97 | 7.21 | 15.42 | 109 | 5.73 | 16.99 | - | - | - |
| | Week 24 Cohort | 184 | 1.96 | 11.68 | 190 | 6.15 | 15.52 | 210 | 6.95 | 18.73 | - | - | - | - | - | - |
| | Week 12 Cohort | 400 | 2.36 | 14.69 | 442 | 5.26 | 18.02 | - | - | - | - | - | - | - | - | - |

n number of patients, SD standard deviation

### 4.2.4 Total cholesterol

This section presents data on changes in total cholesterol observed with quetiapine treatment. The patient groups and data approaches were the same as those described in Section 4.2.1 above.

Across indications—without comparison to placebo

Data presented here are for all samples irrespective of fasting status.

- After approximately six months of treatment with quetiapine mean total cholesterol appeared to increase by at most 5% across the higher dose indications of schizophrenia and bipolar disorder, whereas in MDD and GAD, there appeared to be a mean decrease of approximately 2.5% (Table 13).

Across MDD and GAD

Data presented here are for all fasted samples. Conclusions based on samples irrespective of fasting status are similar.

- Over the 48-week period following randomization, in the randomized withdrawal studies, mean total cholesterol decreased for both quetiapine XR and placebo (Table 14). There was no apparent relationship to dose for mean changes or the proportion of patients with potentially clinically significant values of total cholesterol (Table 14).

- Relative to mean total cholesterol levels reached at the end of the open label phase, subsequent mean cholesterol values appeared to decrease over time in patients whether randomized to continue with quetiapine XR, or to withdraw from quetiapine XR treatment. Mean decreases appeared larger in the quetiapine XR group (Table 15).

**Table 13 Total cholesterol (mg/dL) changes in patients from Pool A (all studies) with at least 12 weeks of quetiapine exposure, by indication**

| | | Monotherapy | | | | | | | | Adjunct therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | | Schizophrenia | | Bipolar disorder monotherapy | | MDD+GAD (pooled) | | Monotherapy Total | | Bipolar disorder (adjunct to lithium or valproate) | |
| ≥12 | n[a] | 1001 | | 1704 | | 1628 | | 4333 | | 1705 | |
| | Baseline mean (SD) | 189.6 | (43.1) | 188.7 | (47.2) | 199.9 | (42.6) | 193.1 | (44.9) | 199.7 | (42.5) |
| | Mean change (SD) | 6.8 | (35.2) | 5.1 | (37.5) | -3.2 | (32.6) | 2.4 | (35.4) | 3.1 | (37.3) |
| | Modal dose (SD) | 634.5 | (265.1) | 510.0 | (182.2) | 169.9 | (92.2) | 410.9 | (264.0) | 501.2 | (138.5) |
| ≥24 | n[a] | 383 | | 922 | | 589 | | 1894 | | 1013 | |
| | Baseline mean (SD) | 186.7 | (40.9) | 190.6 | (46.2) | 202.6 | (43.7) | 193.5 | (44.8) | 199.4 | (41.6) |
| | Mean change (SD) | 9.6 | (38.5) | 4.3 | (37.8) | -5.0 | (34.8) | 2.5 | (37.4) | 3.7 | (39.1) |
| | Modal dose (SD) | 510.7 | (220.4) | 495.0 | (185.6) | 172.5 | (92.7) | 397.8 | (228.5) | 504.0 | (139.1) |

[a] Number of patients with an assessment at baseline and at least one assessment post baseline.
GAD Generalized anxiety disorder; MDD Major depressive disorder; n Number of patients in category; SD Standard deviation

**Table 14 Total cholesterol (mg/dL) change from open-label baseline in Pool E (long term MDD and GAD randomized withdrawal studies)**

| Treatment and dose | | Open label stabilization (all patients receiving QTP XR) | | Randomized withdrawal phase, observed case change from OL baseline | | | | | Patients with potentially clinically significant value, ≥240 mg/dL, n/N (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OL Baseline | End of OL | Randomized Baseline | Week 12 | Week 24 | Week 36 | Week 48 | At randomized baseline/at end of OL (Patients 'normal' at start of OL) | At randomized final |
| Placebo | n | | | 493 | 401 | 168 | 75 | 28 | | |
| | Mean | | | -2.37 | -4.74 | -10.10 | -9.12 | -8.71 | 27/419 (6.4%) | 21/350 (6.0%) |
| | SD | | | 31.66 | 31.50 | 27.15 | 30.49 | 28.80 | | |
| Quetiapine XR ≤100 mg/day | n | | | 109 | 103 | 50 | 29 | 12 | | |
| | Mean | | | -5.73 | -10.94 | -14.38 | -20.66 | -38.75 | 7/89 (7.9%) | 9/86 (10.5%) |
| | SD | | | 29.98 | 27.49 | 29.26 | 42.99 | 44.41 | | |
| Quetiapine XR >100 mg/day to ≤200 mg/day | n | | | 222 | 194 | 91 | 41 | 15 | | |
| | Mean | | | -0.23 | -6.23 | -11.34 | -10.39 | -10.20 | 17/195 (8.7%) | 12/170 (7.1%) |
| | SD | | | 33.62 | 38.88 | 35.05 | 35.24 | 40.75 | | |
| Quetiapine XR >200 mg/day to ≤300 mg/day | n | | | 148 | 128 | 70 | 42 | 15 | | |
| | Mean | | | 1.63 | -5.61 | -4.54 | -10.24 | -20.60 | 10/120 (8.3%) | 7/109 (6.4%) |
| | SD | | | 37.41 | 31.12 | 37.27 | 22.23 | 36.40 | | |
| Quetiapine XR total | n | 2866 | 1460 | 479 | 425 | 211 | 112 | 42 | | |
| | Mean | 199.9 | -2.25 | -0.91 | -7.19 | -9.81 | -12.99 | -22.07 | 34/404 (8.4%) | 28/365 (7.7%) |
| | SD | 42.7 | 32.58 | 34.11 | 34.12 | 34.61 | 33.42 | 41.01 | | |

GAD Generalized anxiety disorder; LOCF Last observation carried forward; MDD Major depressive disorder; N Total number of patients in treatment group; n Number of patients in category; OL Open-label; QTP XR Quetiapine extended-release; SD Standard deviation
Proportion of patients with potentially clinically significant value is not adjusted for the longer exposure in the quetiapine XR treatment group

**Table 15 Total cholesterol (mg/dL) change from open-label baseline in study completion cohorts from Pool E (long term MDD and GAD randomized withdrawal studies)**

| | | Week of Randomised Phase | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Week 0 (Randomisation) | | | Week 12 | | | Week 24 | | | Week 36 | | | Week 48 | | |
| | Completer Cohort | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **Placebo** | Week 48 Cohort | 27 | -6.52 | 29.17 | 26 | -9.92 | 24.74 | 25 | -13.80 | 27.94 | 26 | -12.38 | 34.34 | 28 | -8.71 | 28.80 |
| | Week 36 Cohort | 71 | -7.63 | 25.80 | 66 | -11.73 | 23.09 | 69 | -9.55 | 24.90 | 75 | -9.12 | 30.49 | - | - | - |
| | Week 24 Cohort | 154 | -5.39 | 30.56 | 146 | -8.03 | 33.46 | 168 | -10.10 | 27.15 | - | - | - | - | - | - |
| | Week 12 Cohort | 363 | -2.77 | 29.49 | 401 | -4.74 | 31.50 | - | - | - | - | - | - | - | - | - |
| **Quetiapine XR** | Week 48 Cohort | 38 | -4.05 | 37.63 | 39 | -10.05 | 33.08 | 38 | -12.29 | 38.90 | 38 | -18.39 | 42.50 | 42 | -22.07 | 41.01 |
| | Week 36 Cohort | 98 | -1.84 | 29.04 | 85 | -9.96 | 27.30 | 99 | -11.84 | 35.74 | 112 | -12.99 | 33.42 | - | - | - |
| | Week 24 Cohort | 178 | 0.38 | 32.78 | 170 | -10.77 | 36.44 | 211 | -9.81 | 34.61 | - | - | - | - | - | - |
| | Week 12 Cohort | 373 | -2.47 | 34.25 | 425 | -7.19 | 34.12 | - | - | - | - | - | - | - | - | - |

n number of patients, SD standard deviation

### 4.2.5 High-density lipoprotein

This section presents data on changes in high-density lipoprotein (HDL) observed with quetiapine treatment. The patient groups and data approaches were the same as those described in Section 4.2.1 above.

Across indications—without comparison to placebo

Data presented here are for all samples irrespective of fasting status.

- Across indications, after approximately six months of treatment with quetiapine decreases in HDL appeared to be larger in MDD and GAD (8%) than in the indications of schizophrenia and bipolar disorder (up to 3.0%) (Table 16).

Across MDD and GAD

Data presented here are for all fasted samples. Conclusions based on samples irrespective of fasting status are similar.

- Over the 48-week period following randomization, in the randomized withdrawal studies mean decreases in HDL were larger on quetiapine XR than placebo (Table 17). There was no apparent relationship to dose for mean changes or the proportion of patients with potentially clinically significant values of HDL (Table 17).

- Among patients who were randomized to withdraw from quetiapine XR treatment after the open-label phase, there were no further decreases in HDL, and an indication of some return to open-label baseline over the 48 week post randomization (Table 18).

- Among patients randomized to continue on quetiapine XR, mean HDL values appeared to decrease further over the initial 12 weeks post randomization though, thereafter, there appeared to be little further change (Table 18).

**Table 16 HDL (mg/dL) changes in patients from Pool A (all studies) with at least 12 weeks of quetiapine exposure, by indication**

| | | Monotherapy | | | | | | | | Adjunct therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | | Schizophrenia | | Bipolar disorder monotherapy | | MDD+GAD (pooled) | | Monotherapy Total | | Bipolar disorder (adjunct to lithium or valproate) | |
| ≥12 | n[a] | 765 | | 1703 | | 1628 | | 4096 | | 1706 | |
| | Baseline mean (SD) | 48.0 | (13.3) | 51.1 | (15.1) | 55.7 | (15.6) | 52.4 | (15.2) | 51.0 | (14.6) |
| | Mean change (SD) | 0.3 | (9.6) | -1.7 | (11.4) | -3.8 | (10.1) | -2.1 | (10.7) | -0.4 | (10.4) |
| | Modal dose (SD) | 703.0 | (238.5) | 510.1 | (182.2) | 169.9 | (92.2) | 410.9 | (266.2) | 501.2 | (138.5) |
| ≥24 | n[a] | 202 | | 922 | | 589 | | 1713 | | 1014 | |
| | Baseline mean (SD) | 47.2 | (13.2) | 51.6 | (14.7) | 56.5 | (15.6) | 52.8 | (15.1) | 50.7 | (14.4) |
| | Mean change (SD) | -0.1 | (9.8) | -1.5 | (11.7) | -4.5 | (10.6) | -2.4 | (11.2) | -0.4 | (10.8) |
| | Modal dose (SD) | 623.9 | (162.3) | 495.0 | (185.6) | 172.5 | (92.7) | 399.2 | (230.5) | 503.9 | (139.0) |

[a] Number of patients with an assessment at baseline and at least one assessment post baseline.
GAD Generalized anxiety disorder; MDD Major depressive disorder; n Number of patients in category; SD Standard deviation

**Table 17 HDL (mg/dL) change from open-label baseline in Pool E (long term MDD and GAD randomized withdrawal studies)**

| Treatment and dose | | Open-label stabilization (all patients receiving QTP XR) | | Randomized withdrawal phase, observed case change from OL baseline | | | | | Patients with potentially clinically significant value, ≤40 mg/dL, from OL baseline, n/N (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OL baseline | End of OL | Randomized baseline | Week 12 | Week 24 | Week 36 | Week 48 | At randomized baseline/at end of OL (Patients 'normal' at start of OL) | At randomized final |
| Placebo | n | | | 493 | 401 | 168 | 75 | 28 | | |
| | Mean | | | -3.48 | -3.11 | -2.27 | -0.80 | 0.21 | 55/433 (12.7%) | 46/357 (12.9%) |
| | SD | | | 10.08 | 9.43 | 8.20 | 8.72 | 7.01 | | |
| Quetiapine XR ≤100 mg/day | n | | | 109 | 103 | 50 | 29 | 12 | | |
| | Mean | | | -3.10 | -4.15 | -3.28 | -1.90 | -12.17 | 8/98 (8.2%) | 10/96 (10.4%) |
| | SD | | | 8.11 | 9.96 | 12.92 | 12.35 | 10.91 | | |
| Quetiapine XR >100 mg/day to ≤200 mg/day | n | | | 222 | 194 | 91 | 41 | 15 | | |
| | Mean | | | -3.91 | -5.23 | -6.73 | -5.51 | -6.33 | 31/195 (15.9%) | 39/179 (21.8%) |
| | SD | | | 9.62 | 10.84 | 9.09 | 7.81 | 7.35 | | |
| Quetiapine XR >200 mg/day to ≤300 mg/day | n | | | 148 | 129 | 70 | 42 | 15 | | |
| | Mean | | | -3.26 | -4.68 | -4.24 | -4.57 | -2.60 | 15/123 (12.2%) | 15/109 (13.8%) |
| | SD | | | 10.88 | 8.79 | 9.76 | 7.74 | 5.08 | | |
| Quetiapine XR total | n | 2864 | 1459 | 479 | 426 | 211 | 112 | 42 | | |
| | Mean | 55.45 | -3.27 | -3.52 | -4.80 | -5.09 | -4.22 | -6.67 | 54/416 (13.0%) | 64/384 (16.7%) |
| | SD | 15.54 | 9.81 | 9.71 | 10.03 | 10.39 | 9.20 | 8.61 | | |

GAD Generalized anxiety disorder; LOCF Last observation carried forward; MDD Major depressive disorder; N Total number of patients in treatment group; n Number of patients in category; OL Open-label; QTP XR Quetiapine extended-release; SD Standard deviation
Proportion of patients with potentially clinically significant value is not adjusted for the longer exposure in the quetiapine XR treatment group

**Table 18 HDL (mg/dL) change from open-label baseline in study completion cohorts from Pool E (long term MDD and GAD randomized withdrawal studies)**

| | | Week of Randomised Phase | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Week 0 (Randomisation) | | | Week 12 | | | Week 24 | | | Week 36 | | | Week 48 | | |
| | Completer Cohort | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **Placebo** | Week 48 Cohort | 27 | -1.37 | 6.17 | 26 | 0.85 | 6.02 | 25 | -0.96 | 6.48 | 26 | 0.85 | 8.38 | 28 | 0.21 | 7.01 |
| | Week 36 Cohort | 71 | -1.51 | 8.41 | 66 | -1.27 | 8.59 | 69 | -1.16 | 9.36 | 75 | -0.80 | 8.72 | - | - | - |
| | Week 24 Cohort | 154 | -2.76 | 7.34 | 146 | -2.38 | 8.15 | 168 | -2.27 | 8.20 | - | - | - | - | - | - |
| | Week 12 Cohort | 363 | -3.21 | 8.58 | 401 | -3.11 | 9.43 | - | - | - | - | - | - | - | - | - |
| **Quetiapine XR** | Week 48 Cohort | 38 | -1.11 | 7.21 | 39 | -3.41 | 6.73 | 38 | -6.11 | 7.00 | 38 | -5.08 | 7.81 | 42 | -6.67 | 8.61 |
| | Week 36 Cohort | 98 | -1.83 | 7.03 | 85 | -3.80 | 8.69 | 99 | -5.32 | 11.82 | 112 | -4.22 | 9.20 | - | - | - |
| | Week 24 Cohort | 178 | -2.72 | 7.78 | 170 | -5.54 | 10.17 | 211 | -5.09 | 10.39 | - | - | - | - | - | - |
| | Week 12 Cohort | 374 | -3.58 | 8.43 | 426 | -4.80 | 10.03 | - | - | - | - | - | - | - | - | - |

n number of patients, SD standard deviation

### 4.2.6 Low-density lipoprotein

This section presents data on changes in low-density lipoprotein (LDL) observed with quetiapine treatment. The patient groups and data approaches were the same as those described in Section 4.2.1 above.

Across indications—without comparison to placebo

- In a comparison across indications, after approximately six months of treatment with quetiapine there was an approximate 4% decrease in LDL in MDD and GAD with no consistent change in the schizophrenia and bipolar disorder groups (Table 19).

Across MDD and GAD

- Over the 48-week period following randomization, in the randomized withdrawal studies, the decreases in LDL were numerically larger on quetiapine XR than on placebo (Table 20). The proportions of patients with potentially clinically significant values of LDL were similar between quetiapine XR and placebo. There was no apparent relationship to dose for mean changes or the proportion of patients with potentially clinically significant values of LDL (Table 20).

- Among patients who were randomized to withdraw from quetiapine XR treatment after the open label phase, there were no further decreases in mean LDL over the 48-week randomized treatment period (Table 21).

- Among patients who were randomized to continue with quetiapine XR treatment after the open label phase, mean LDL values appeared to continue to decrease over the 48-week randomized treatment period (Table 21).

**Table 19 LDL (mg/dL) changes in patients from Pool A (all studies) with at least 12 weeks of quetiapine exposure, by indication**

| | | Monotherapy | | | | | | | | Adjunct therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | | Schizophrenia | | Bipolar disorder monotherapy | | MDD+GAD (pooled) | | Monotherapy Total | | Bipolar disorder (adjunct to lithium or valproate) | |
| ≥12 | n[a] | 323 | | 1064 | | 1028 | | 2415 | | 796 | |
| | Baseline mean (SD) | 112.8 | (34.9) | 108.8 | (40.0) | 117.9 | (36.0) | 113.2 | (37.9) | 116.2 | (36.6) |
| | Mean change (SD) | -0.6 | (28.4) | 4.6 | (30.6) | -3.0 | (26.9) | 0.7 | (29.0) | -1.6 | (31.5) |
| | Modal dose (SD) | 642.7 | (158.5) | 507.0 | (184.0) | 176.3 | (94.0) | 384.4 | (236.7) | 502.3 | (140.0) |
| ≥24 | n[a] | 69 | | 607 | | 414 | | 1090 | | 501 | |
| | Baseline mean (SD) | 109.1 | (34.5) | 110.1 | (38.4) | 119.1 | (37.0) | 113.5 | (37.8) | 117.2 | (36.9) |
| | Mean change (SD) | 1.0 | (31.5) | 4.1 | (30.4) | -4.6 | (27.1) | 0.6 | (29.5) | -3.1 | (32.9) |
| | Modal dose (SD) | 662.3 | (147.6) | 485.7 | (187.8) | 181.6 | (92.9) | 381.4 | (224.7) | 496.5 | (137.6) |

[a] Number of patients with an assessment at baseline and at least one assessment post baseline.
GAD Generalized anxiety disorder; MDD Major depressive disorder; n Number of patients in category; SD Standard deviation

**Table 20 LDL (mg/dL) change from open-label baseline in Pool E (long term MDD and GAD randomized withdrawal studies)**

| Treatment and dose | | Open-label stabilization (all patients receiving QTP XR) | | Randomized withdrawal phase, observed case change from OL baseline | | | | | Patients with potentially clinically significant value, ≥160 mg/dL, Baseline n/N (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OL baseline | End of OL | Randomized baseline | Week 12 | Week 24 | Week 36 | Week 48 | At randomized baseline/at end of OL (Patients 'normal' at start of OL) | At randomized final |
| Placebo | n | | | 493 | 400 | 168 | 75 | 28 | | |
| | Mean | | | -0.40 | -0.77 | -5.84 | -6.99 | -8.00 | 23/443 (5.2%) | 18/371 (4.9%) |
| | SD | | | 27.34 | 27.50 | 23.55 | 22.82 | 25.45 | | |
| Quetiapine XR ≤100 mg/day | n | | | 109 | 103 | 50 | 29 | 12 | | |
| | Mean | | | -3.40 | -7.42 | -10.58 | -18.69 | -30.33 | 6/96 (6.3%) | 5/93 (5.4%) |
| | SD | | | 25.62 | 22.69 | 28.76 | 39.03 | 42.60 | | |
| Quetiapine XR >100 mg/day to ≤200 mg/day | n | | | 222 | 194 | 91 | 41 | 15 | | |
| | Mean | | | -1.18 | -4.79 | -7.13 | -8.51 | -7.53 | 13/198 (6.6%) | 9/177 (5.1%) |
| | SD | | | 28.08 | 31.77 | 31.47 | 33.24 | 30.62 | | |
| Quetiapine XR >200 mg/day to ≤300 mg/day | n | | | 148 | 127 | 70 | 42 | 15 | | |
| | Mean | | | 3.05 | -3.23 | -0.30 | -6.57 | -17.53 | 8/130 (6.2%) | 10/118 (8.5%) |
| | SD | | | 30.01 | 29.80 | 28.96 | 21.68 | 38.79 | | |
| Quetiapine XR total | n | 2863 | 1456 | 479 | 424 | 211 | 112 | 42 | | |
| | Mean | 116.76 | -1.41 | -0.38 | -4.96 | -5.68 | -10.42 | -17.62 | 27/424 (6.4%) | 24/388 (6.2%) |
| | SD | 36.41 | 27.45 | 28.21 | 29.18 | 30.15 | 31.32 | 37.49 | | |

GAD Generalized anxiety disorder; LDL Low-density lipoprotein; LOCF Last observation carried forward; MDD Major depressive disorder; N Total number of patients in treatment group; n Number of patients in category; OL Open-label; QTP XR Quetiapine extended-release; SD Standard deviation
Proportion of patients with potentially clinically significant value is not adjusted for the longer exposure in the quetiapine XR treatment group

**Table 21 LDL (mg/dL) change from open-label baseline in study completion cohorts from Pool E (long term MDD and GAD randomized withdrawal studies)**

| | | Week of Randomised Phase | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Completer Cohort | Week 0 (Randomisation) | | | Week 12 | | | Week 24 | | | Week 36 | | | Week 48 | | |
| | | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **Placebo** | Week 48 Cohort | 27 | -7.63 | 23.94 | 25 | -8.68 | 21.98 | 25 | -11.44 | 23.75 | 26 | -10.77 | 24.24 | 28 | -8.00 | 25.45 |
| | Week 36 Cohort | 71 | -6.13 | 22.18 | 65 | -6.66 | 19.25 | 69 | -6.80 | 22.24 | 75 | -6.99 | 22.82 | - | - | - |
| | Week 24 Cohort | 154 | -2.85 | 26.42 | 145 | -2.58 | 29.35 | 168 | -5.84 | 23.55 | - | - | - | - | - | - |
| | Week 12 Cohort | 362 | -0.80 | 25.42 | 400 | -0.77 | 27.50 | - | - | - | - | - | - | - | - | - |
| **Quetiapine XR** | Week 48 Cohort | 38 | -7.92 | 31.93 | 39 | -9.49 | 31.34 | 38 | -8.82 | 36.31 | 38 | -16.21 | 37.94 | 42 | -17.62 | 37.49 |
| | Week 36 Cohort | 98 | -4.47 | 27.23 | 85 | -8.81 | 25.57 | 99 | -7.74 | 32.18 | 112 | -10.42 | 31.32 | - | - | - |
| | Week 24 Cohort | 178 | -2.20 | 28.74 | 169 | -8.28 | 31.03 | 211 | -5.68 | 30.15 | - | - | - | - | - | - |
| | Week 12 Cohort | 372 | -1.87 | 28.19 | 424 | -4.96 | 29.18 | - | - | - | - | - | - | - | - | - |

n number of patients, SD standard deviation

### 4.2.7 Triglycerides

This section presents data on changes in triglycerides observed with quetiapine treatment. The patient groups and data approaches were the same as those described in Section 4.2.1 above.

Across indications—without comparison to placebo

- After approximately six months of treatment with quetiapine, used as a monotherapy, mean increases in triglycerides of up to approximately 8% were seen across all indications. A larger mean increase was seen when quetiapine was used as an adjunct to lithium or valproate in bipolar disorder (Table 22).

Across MDD and GAD

- Over the 48-week period following randomization in the randomized withdrawal studies, decreases in mean triglycerides were seen in patients randomized to continue with quetiapine XR; mean decreases were also seen in patients randomized to discontinue quetiapine XR (Table 23). The proportion of patients with potentially clinically significant values was higher on quetiapine XR (Table 23). There was no apparent relationship to dose for mean changes or the proportion of patients with potentially clinically significant values of triglycerides (Table 23).

- Among patients randomized to withdraw from quetiapine XR treatment after the open-label phase, mean triglycerides levels returned toward open-label baseline levels over the 48-week randomized treatment period (Table 24).

**Table 22 Triglycerides (mg/dL) changes in patients from Pool A (all studies) with at least 12 weeks of quetiapine exposure, by indication**

| | | Monotherapy | | | | | | | | Adjunct therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | | Schizophrenia | | Bipolar disorder monotherapy | | MDD+GAD (pooled) | | Monotherapy Total | | Bipolar disorder (adjunct to lithium or valproate) | |
| ≥12 | n[a] | 325 | | 1068 | | 1031 | | 2424 | | 799 | |
| | Baseline mean (SD) | 137.9 | (84.6) | 147.2 | (108.0) | 143.7 | (104.4) | 144.5 | (103.6) | 166.0 | (107.7) |
| | Mean change (SD) | 14.5 | (96.6) | 13.6 | (111.2) | 12.4 | (87.3) | 13.2 | (99.7) | 29.7 | (138.2) |
| | Modal dose (SD) | 642.2 | (159.4) | 506.6 | (183.9) | 176.0 | (94.1) | 384.2 | (236.7) | 502.7 | (140.3) |
| ≥24 | n[a] | 69 | | 609 | | 414 | | 1092 | | 502 | |
| | Baseline mean (SD) | 138.5 | (82.7) | 148.8 | (111.0) | 146.9 | (101.9) | 147.5 | (106.0) | 168.6 | (103.7) |
| | Mean change (SD) | 1.4 | (82.8) | 12.4 | (115.3) | 1.6 | (86.8) | 7.6 | (103.5) | 33.7 | (157.6) |
| | Modal dose (SD) | 662.3 | (147.6) | 485.7 | (187.5) | 181.6 | (92.9) | 381.6 | (224.6) | 496.3 | (137.5) |

[a] Number of patients with an assessment at baseline and at least one assessment post baseline.
GAD Generalized anxiety disorder; MDD Major depressive disorder; n Number of patients in category; SD Standard deviation

**Table 23 Triglycerides (mg/dL) change from open-label baseline in Pool E (long term MDD and GAD randomized withdrawal studies)**

| Treatment and dose | | Open-label stabilization (all patients receiving QTP XR) | | Randomized withdrawal phase, observed case change from OL baseline | | | | | Patients with potentially clinically significant value, ≥200 mg/dL, n/N (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OL baseline | End of OL | Randomized baseline | Week 12 | Week 24 | Week 36 | Week 48 | At randomized baseline/at end of OL (Patients 'normal' at start of OL) | At randomized final |
| Placebo | n | | | 493 | 401 | 168 | 75 | 28 | | |
| | Mean | | | 9.59 | -3.12 | -11.52 | -9.12 | -4.07 | 50/411 (12.2%) | 34/342 (9.9%) |
| | SD | | | 85.81 | 77.19 | 69.00 | 90.06 | 67.69 | | |
| Quetiapine XR ≤100 mg/day | n | | | 109 | 103 | 50 | 29 | 12 | | |
| | Mean | | | 0.43 | 0.74 | -7.54 | -1.86 | 3.83 | 6/90 (6.7%) | 7/90 (7.8%) |
| | SD | | | 55.18 | 79.20 | 64.57 | 65.12 | 88.67 | | |
| Quetiapine XR >100 mg/day to ≤200 mg/day | n | | | 222 | 194 | 91 | 41 | 15 | | |
| | Mean | | | 28.01 | 18.24 | 14.49 | 17.93 | 18.13 | 33/188 (17.6%) | 28/164 (17.1%) |
| | SD | | | 104.75 | 76.97 | 62.42 | 49.27 | 60.90 | | |
| Quetiapine XR >200 mg/day to ≤300 mg/day | n | | | 148 | 128 | 70 | 42 | 15 | | |
| | Mean | | | 7.16 | 8.81 | 1.23 | 5.17 | -2.00 | 23/119 (19.3%) | 14/102 (13.7%) |
| | SD | | | 91.43 | 80.18 | 116.02 | 76.88 | 44.95 | | |
| Quetiapine XR total | n | 2866 | 1460 | 479 | 425 | 211 | 112 | 42 | | |
| | Mean | 142.08 | 14.40 | 15.29 | 11.16 | 4.87 | 8.02 | 6.86 | 62/397 (15.6%) | 49/356 (13.8%) |
| | SD | 103.08 | 92.76 | 92.07 | 78.63 | 84.54 | 64.75 | 64.37 | | |

GAD Generalized anxiety disorder; LOCF Last observation carried forward; MDD Major depressive disorder; N Total number of patients in treatment group; n Number of patients in category; OL Open label; QTP XR Quetiapine extended-release; SD Standard deviation
Proportion of patients with potentially clinically significant value is not adjusted for the longer exposure in the quetiapine XR treatment group

**Table 24 Triglycerides (mg/dL) change from open-label baseline in study completion cohorts from Pool E (long term MDD and GAD randomized withdrawal studies)**

| | | Week of Randomised Phase | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Completer Cohort | Week 0 (Randomisation) | | | Week 12 | | | Week 24 | | | Week 36 | | | Week 48 | | |
| | | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD | n | Mean | SD |
| **Placebo** | Week 48 Cohort | 27 | 12.74 | 60.78 | 26 | -6.46 | 57.46 | 25 | -6.52 | 59.99 | 26 | -12.62 | 69.15 | 28 | -4.07 | 67.69 |
| | Week 36 Cohort | 71 | -0.10 | 76.58 | 66 | -20.23 | 74.70 | 69 | -10.22 | 74.92 | 75 | -9.12 | 90.06 | - | - | - |
| | Week 24 Cohort | 154 | 2.53 | 73.81 | 146 | -15.86 | 71.13 | 168 | -11.52 | 69.00 | - | - | - | - | - | - |
| | Week 12 Cohort | 363 | 9.12 | 77.75 | 401 | -3.12 | 77.19 | - | - | - | - | - | - | - | - | - |
| **Quetiapine XR** | Week 48 Cohort | 38 | 26.97 | 76.27 | 39 | 15.46 | 88.63 | 38 | 16.68 | 119.11 | 38 | 12.97 | 66.37 | 42 | 6.86 | 64.37 |
| | Week 36 Cohort | 98 | 23.42 | 101.76 | 85 | 12.28 | 82.37 | 99 | 7.04 | 102.78 | 112 | 8.02 | 64.75 | - | - | - |
| | Week 24 Cohort | 178 | 28.53 | 105.64 | 170 | 12.56 | 83.57 | 211 | 4.87 | 84.54 | - | - | - | - | - | - |
| | Week 12 Cohort | 373 | 15.21 | 92.96 | 425 | 11.16 | 78.63 | - | - | - | - | - | - | - | - | - |

n number of patients, SD standard deviation

### 4.2.8 Analysis of adverse events

A review of adverse events in the consolidated clinical study database was conducted using 4 study pools:

- Pool A: All studies
- Pool B: Placebo-controlled short-term studies
- Pool C: All long-term randomized withdrawal studies
- Pool E: Long-term MDD and GAD randomized withdrawal studies

Adverse events were summarised across studies as follows:

- Firstly, to account for all studies irrespective of design, placebo control, or blinding, simple pooling of data has been used to provide descriptive event and exposure totals for quetiapine, placebo, and comparator groups across studies. This simple pooling of data was applied to Pool A, and no allowance is made for the data arising in different studies, and so formal comparison for relative risks between treatment groups is not possible.
- Secondly, when examining data from pools other than Pool A, a stratified analysis was used which combines the data differently, allowing for possible differences between studies and thus allows event rates to be compared for the relative risk between treatment quetiapine and placebo groups.

In these stratified analyses, data were combined across studies using the Mantel-Haenszel approach to estimate the overall relative risk according to Breslow and Day 1987. This approach allows for differing exposure times between treatment groups. The 95% confidence intervals were provided according to the method described by Robins et al 1986. When the overall total number of events across studies was very few, exact methods were used to estimate the overall relative risk and associated 95% confidence interval.

**Presentation of individual study data**

For the purposes of individual study data display, a descriptive 95% credibility interval for the relative risk was provided using the method of Barker and Caldwell 2008 with an uninformative uniform prior; the median of the posterior distribution was used to provide a point estimate for the relative risk within a individual study. These intervals were provided to account for individual studies in which no events were observed, as the interval is calculable even when the number of events within each treatment group is zero. The credibility interval quickly converges with the conventional asymptotic CI for the event rate ratio as the number of events increases.

**Visual display of individual study and overall relative risk estimates**

Throughout this document, adverse event results are displayed visually along with individual study data in a forest plot format (see Figure 7, Figure 8, Figure 9, Figure 10, and Figure 11). Each study in the forest plot is labeled by both the study number and the number of events/total exposure in patient-years in the quetiapine group versus the number of events/total exposure in years in the placebo group. For the individual studies, 95% credibility intervals are presented to ensure all studies are accounted for, including those in which no events were observed.

#### 4.2.8.1 Adverse events potentially related to diabetes mellitus

The clinical studies database was searched for adverse events potentially related to diabetes mellitus. The events were not clinically adjudicated, and patients with evidence of diabetes at entry into the studies were not excluded from the initial analysis.

Table 25 presents the incidence and relative risk estimates for each of the 4 pools described above. A summary of all events is provided in Appendix B, Table 43, Table 44, and Table 45. Figure 7 presents relative risk estimates for adverse events potentially related to diabetes mellitus in all placebo-controlled studies (Pool B).

Within Pool B there were 38 events observed during quetiapine treatment and 23 on placebo. The Mantel-Haenszel relative risk estimate was 0.87 (95% CI 0.51 to 1.48).

Within Pool C there were 31 events observed during quetiapine treatment and 11 events observed during placebo treatment. Of these events, 14 (10 on quetiapine and 4 on placebo) occurred in patients who had evidence of diabetes reported prior to the start of the open-label phases of the long-term randomized withdrawal studies. The Mantel-Haenszel relative risk estimate was 1.98 (95% CI 1.00 to 3.95). This confidence interval overlaps with the CI based on data from Pool B. An additional summary excluding all patients with evidence of diabetes at baseline was conducted. The Mantel-Haenszel relative risk estimate was 2.11 (95% CI 0.90 to 4.98), consistent with the overall analysis.

Within Pool E (long term MDD and GAD randomized withdrawal studies), there were 7 events observed during quetiapine XR treatment and 5 events observed during placebo treatment. The Mantel-Haenszel relative risk estimate was 1.01 (95% CI 0.32 to 3.17).

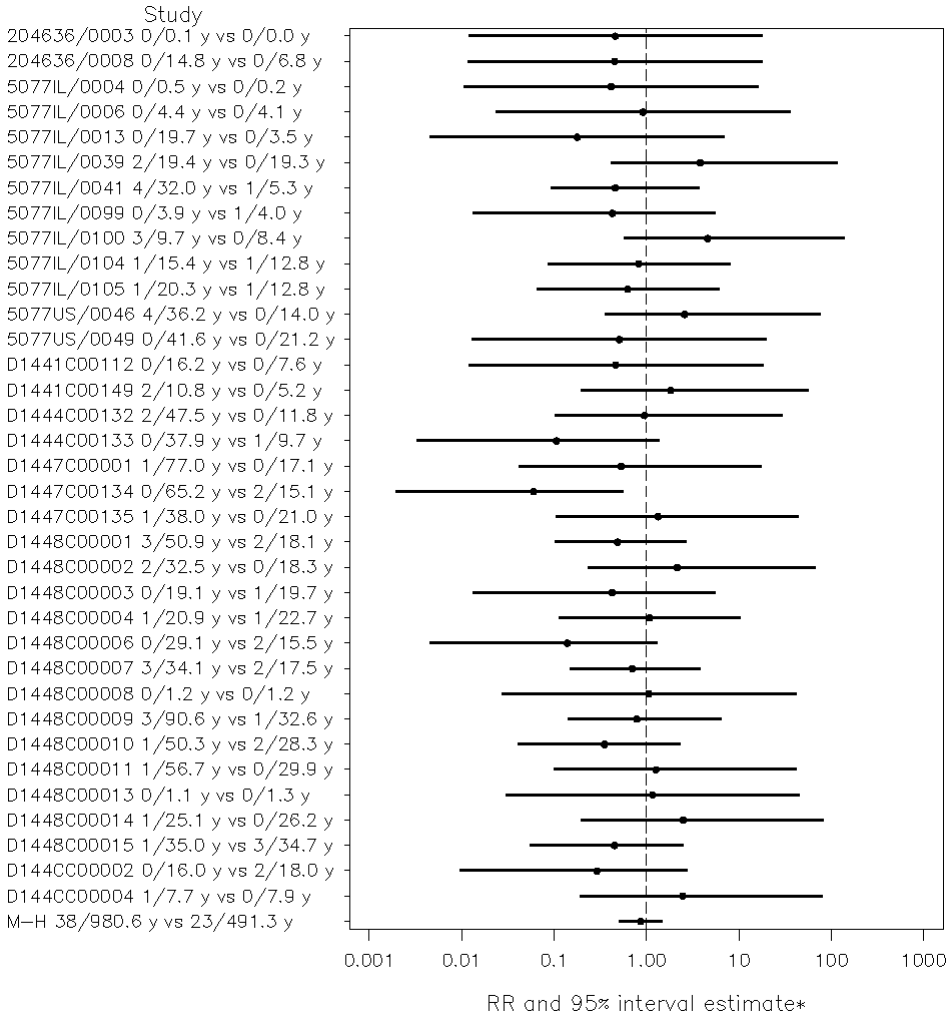
Figure 7 and Figure 8 present relative risk estimates for adverse events potentially related to diabetes mellitus from each study in Pool B and Pool C. Considering all the available clinical study data, there is no consistent pattern for an increased risk of adverse events potentially related to diabetes with quetiapine relative to placebo.

**Table 25 Incidence and relative risk of adverse events potentially related to diabetes mellitus**

| Treatment | Patients with event | Total patients[a] | Exposure[b] | Incidence density[c] | MH incidence rate per 100 pt-yrs[d] | MH relative risk[e] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|
| Pool A (all studies) | | | | | | | | |
| QTP | 199 | 26454 | 7843.0 | 2.5 | | | | |
| Pla | 34 | 6375 | 1193.7 | 2.8 | | | | |
| Pool B (Placebo-controlled short-term studies) | | | | | | | | |
| QTP | 38 | 8853 | 980.6 | | 4.1 | 0.87 | 0.51 | 1.48 |
| Pla | 23 | 4359 | 491.3 | | 4.7 | | | |
| Pool C (All long-term randomized withdrawal studies) | | | | | | | | |
| QTP | 31 | 2043 | 1017.5 | | 3.1 | 1.98 | 1.00 | 3.95 |
| Pla | 11 | 2016 | 702.4 | | 1.5 | | | |
| Pool E (long term MDD and GAD randomized withdrawal studies) | | | | | | | | |
| QTP | 7 | 607 | 240.8 | | 2.9 | 1.01 | 0.32 | 3.17 |
| Pla | 5 | 601 | 172.9 | | 2.9 | | | |

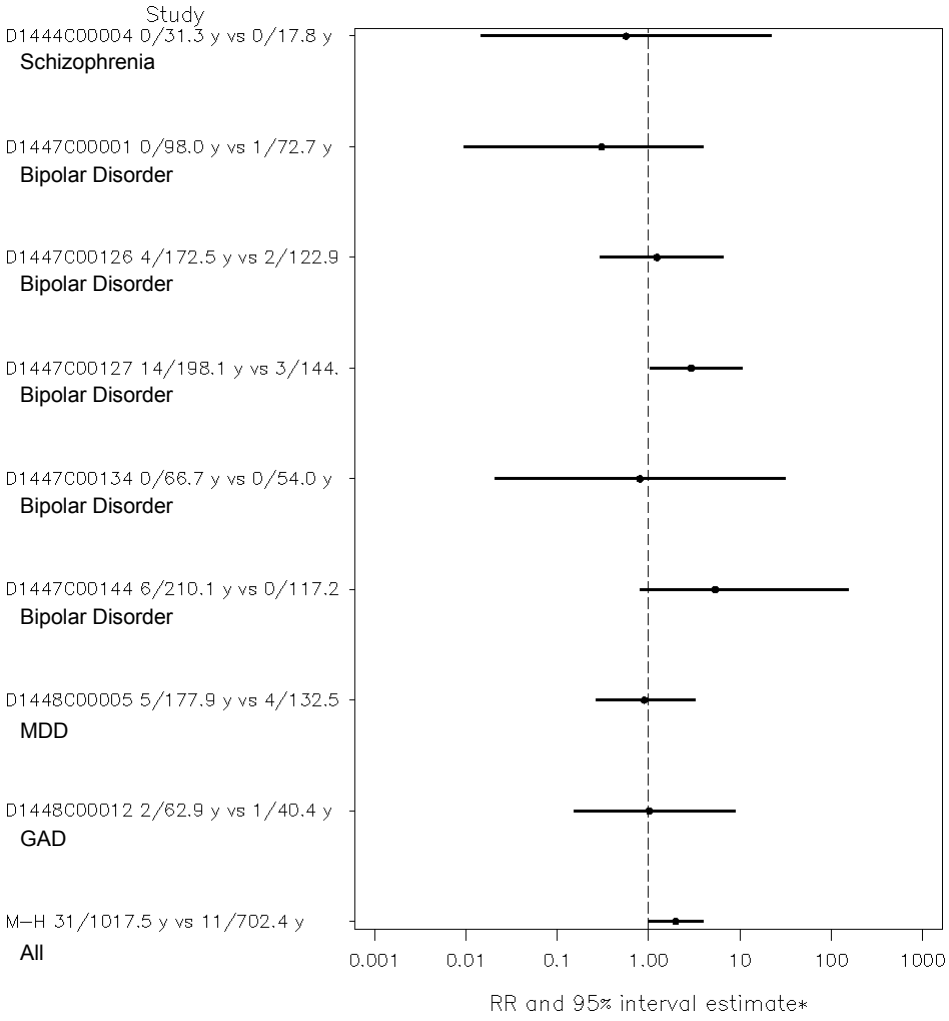
[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years.
[c] 100 x total number of patients with event/total patient years of exposure.
[d] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[e] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Adverse events were not clinically adjudicated.

**Figure 7** **Forest plot of Mantel-Haenszel relative risk estimates and 95% credibility intervals of adverse events potentially related to diabetes mellitus in Pool B (placebo-controlled studies)**




*Overall RR and 95% CI from M-H analysis. Individual study data are 95% credibility intervals

**Figure 8** **Forest plot of Mantel-Haenszel relative risk estimates and 95% credibility intervals of adverse events potentially related to diabetes mellitus in Pool C (all long-term randomized withdrawal studies)**




*Overall RR and 95% CI from M-H analysis. Individual study data are 95% credibility intervals

## Conclusions on adverse events potentially related to DM

An increased number of adverse events potentially related to diabetes was reported in the long term randomized withdrawal studies, but not in the placebo-controlled short term studies. These events were not clinically adjudicated, and patients with evidence of diabetes at entry into the studies were not excluded from the initial analysis. The risk of adverse events potentially related to diabetes with quetiapine XR treatment in long-term randomized withdrawal studies of patients with MDD or GAD was 1.01 (95% CI 0.32-3.17). Considering all of the available clinical study data, there is no consistent trend for an increased risk of adverse events potentially related to diabetes with quetiapine relative to placebo.

#### 4.2.8.2 Adverse events potentially related to atherosclerotic cardiovascular disease

A review of the consolidated clinical study database was conducted, searching for adverse events potentially related to atherosclerotic cardiovascular disease. This group of terms was selected to try to capture major cardiovascular events, i.e. cardiovascular death, fatal and nonfatal MI, fatal and nonfatal stroke and is believed to relate to atherosclerosis where dyslipidemia and metabolic disturbances are part of the pathogenesis.

Table 46 presents the incidence and relative risk estimates for each of the 4 pools described above. A summary of all events is provided in Appendix B.

Within the overall clinical study program and the MDD/GAD studies, there was no evidence that quetiapine XR was associated with adverse events potentially related to atherosclerotic cardiovascular disease.

**AERS data on adverse events potentially related to atherosclerotic cardiovascular disease with quetiapine treatment**

The FDA's Adverse Event Reporting System (AERS) database was searched through the third quarter of 2008. Using post-marketing data sets, different quantitative signal detection tools can be employed to search for a possible association between a drug and an event. Any identified potential signals require further investigation given the limitations of the tools and the data upon which they are based. AstraZeneca obtained data for quetiapine IR or quetiapine XR using the AERS database.

The signal detection method utilized the MGPS algorithm. This quantifies potential drug-event associations by producing a set of scores, which can be ranked to indicate varying strengths of reporting relationships between drugs and events. These scores, denoted the Empirical Bayes Geometric Mean (EBGM), estimate the relative reporting ratio of an event for a particular drug relative to all other drugs in the database being analyzed. Lower and upper 90% confidence intervals for EBGM values are denoted EB05 and EB95 respectively. An EB05 $\geq$1.8 suggests that there is a possible association between the drug and event.

A review of the AERS database for events related to ischemic heart disease, myocardial infarction, and cerebrovascular events did not show a signal for quetiapine.

**Conclusions on adverse events potentially related to atherosclerotic cardiovascular disease**

Within the overall clinical study program and the MDD/GAD studies, there was no evidence that quetiapine was associated with adverse events potentially related to atherosclerotic cardiovascular disease. In addition, no signal was detected in a review of the AERS database.

**Table 26 Incidence and relative risk of adverse events potentially related to atherosclerotic cardiovascular disease: All cause death, excluding completed suicide and homicide, plus patients with events included in SMQ - Narrow MI or SMQ - Broad CVA, excluding dysarthria**

| Treatment | Patients with event | Total patients[a] | Exposure[b] | Incidence density[c] | MH incidence rate per 100 pt-yrs[d] | MH relative risk[e] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|
| Pool A (all studies) | | | | | | | | |
| QTP | 149 | 26454 | 7889.97 | 1.9 | | | | |
| Pla | 29 | 6375 | 1196.69 | 2.4 | | | | |
| Pool B (Placebo-controlled short-term studies) | | | | | | | | |
| QTP | 32 | 8853 | 981.74 | | 3.36 | 0.73 | 0.42 | 1.25 |
| Pla | 24 | 4359 | 492.41 | | 4.63 | | | |
| Pool C (All long-term randomized withdrawal studies) | | | | | | | | |
| QTP | 1 | 2043 | 1025.95 | | 0.10 | 0.14 | 0.02 | 1.21 |
| Pla | 5 | 2016 | 704.27 | | 0.71 | | | |
| Pool E (Long-term MDD and GAD randomized withdrawal studies) | | | | | | | | |
| QTP | 0 | 607 | 242.02 | | 0.00 | 0.00 | NA | NA |
| Pla | 1 | 601 | 173.74 | | 0.57 | | | |

[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years.
[c] 100 x total number of patients with event/total patient years of exposure.
[d] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[e] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Adverse events terms were not clinically adjudicated

### 4.2.9 Glucose metabolism study (Study 125)

Study 125 was designed to evaluate differential changes in glucose tolerance in patients with schizophrenia, randomized to 24 weeks of treatment with olanzapine, quetiapine, or risperidone.

#### 4.2.9.1 Study design of Study 125

The primary objective was to compare the safety/tolerability profile of quetiapine and olanzapine on glucose metabolism by evaluating the change from randomisation at Week 24 in Area Under the Curve (AUC) $_{0\text{-}2h}$ of the plasma glucose values following Oral Glucose Tolerance Test (OGTT).

Key design strengths include sensitive measures of glucose metabolism, confirmed fasting conditions (patients were hospitalized overnight to ensure 8-14 h fasting conditions prior to OGTT), rigorous screening methods, and a patient sample not previously exposed for at least 90 days to any of the agents under testing. In addition, randomization was stratified by baseline BMI. However, the absence of a placebo group may limit interpretation.

Mean doses at week 24 were: quetiapine, 607.0 mg/day; olanzapine, 15.2 mg/day; and risperidone, 5.2 mg/day.

The primary endpoint, and key secondary parameters are presented in Table 27.

Mean change from baseline to Week 24 in AUC plasma glucose (mg/dL × h) was +9.1 (95% CI -2.3, 20.5) with quetiapine. The primary analysis results indicated that the difference in mean change from baseline in AUC 0-2 h plasma glucose was significantly different between quetiapine and olanzapine (p=0.048) with the quetiapine group showing a smaller mean increase from baseline.

#### 4.2.9.2 Summary of Study 125

The study results suggest that there were differential effects between the investigational products in how the patients in the respective treatment groups responded to stress condition provided by glucose load (OGTT). At Week 24, there was a statistically significant difference between the quetiapine and olanzapine groups in post-load glucose levels as measured by the $AUC_{0\text{-}2h}$ of plasma glucose values, with the quetiapine group showing a smaller mean increase from baseline (randomization) than the olanzapine group.

Though this study was not conducted in an MDD/GAD population, the lack of a statistically significant increase from baseline in the OGTT in a well-controlled study, when quetiapine was dosed at higher levels than would be used in patients with MDD/GAD, is considered relevant.

**Table 27 Fasting plasma glucose and two-hour glucose, change from randomization – Study 125**

| | | Quetiapine | Olanzapine | Risperidone |
|---|---|---|---|---|
| **Primary Endpoint** | | | | |
| AUC plasma glucose value (mg/dL x h) | | | | |
| n | | 111 | 144 | 130 |
| Randomization | Mean (SD) | 255.1 (54.4) | 260.9 (69.1) | 259.3 (65.4) |
| Change at Week 24 | LS mean (SE) | 9.1 (5.8) | 21.9 (5.3) | 18.8 (5.4) |
| | 95% CI | -2.3, 20.5 | 11.5, 32.4 | 8.1, 29.4 |
| **Secondary Endpoints** | | | | |
| Fasting plasma glucose (mg/dL) | | | | |
| n | | 113 | 143 | 132 |
| Randomization | Mean (SD) | 92.6 (12.1) | 93.7 (17.8) | 93.7 (11.9) |
| Change at Week 24 | LS mean (SE) | 3.2 (1.5) | 2.3 (1.4) | 4.4 (1.4) |
| | 95% CI | 0.2, 6.1 | -0.4, 5.1 | 1.6, 7.2 |
| Two-hour glucose (mg/dL) | | | | |
| n | | 109 | 145 | 128 |
| Randomization | Mean (SD) | 106.9 (33.6) | 111.0 (42.1) | 112.9 (38.3) |
| Change at Week 24 | LS mean (SE) | -1.9 (4.1) | +9.8 (3.8) | +10.6 (3.9) |
| | 95% CI | -10.0, 6.3 | 2.4, 17.2 | 2.9, 18.2 |

SD standard deviation, SE standard error, CI confidence interval, n number of patients

### 4.2.10 Overall conclusions on potential long term metabolic risks in patients with MDD or GAD

The current labeling for quetiapine and quetiapine XR contains warnings for hyperglycemia, diabetes, weight gain, and hyperlipidemia, for the higher dose indications of schizophrenia and bipolar disorder.

- ***Within the MDD/GAD program, where lower daily doses are used (50 to 300 mg/day), the mean changes in metabolic variables appeared generally similar to, or smaller than, those seen in studies in indications using higher doses (up to 800 mg/day).***

- ***Within the overall clinical study program and the MDD/GAD studies, there was no evidence that quetiapine XR was associated with adverse events potentially related to atherosclerotic cardiovascular disease.*** In addition, no signal was detected in a review of the AERS database.

- ***Considering all of the available clinical study data, there was no consistent trend for increasing risk of adverse events potentially related to diabetes with quetiapine.*** Within the MDD/GAD studies there was no evidence that quetiapine

XR was associated with adverse events potentially related to diabetes. An increased number of adverse events potentially related to diabetes was reported in the long-term randomized withdrawal studies, but not in the placebo-controlled short term studies.

- ***Evaluation of metabolic data from the MDD and GAD populations did not reveal any metabolic findings or suggest potential long term metabolic risks inconsistent with those seen in the currently approved indications of schizophrenia and bipolar disorder.***

## 4.3 Tardive dyskinesia

### 4.3.1 Introduction

Tardive dyskinesia (TD) is a hyperkinetic movement disorder that has been associated with dopamine and non-dopamine receptor blocking drugs. TD appears in the current label of quetiapine (see Appendix E) as a potential risk with treatment. This warning exists for all antipsychotic medications. Tardive dyskinesia is listed in the label (mostly as post marketing experience) of a number of non-antipsychotic drugs that are used to treat MDD and GAD (aripiprazole, amitriptyline, trazodone, venlafaxine, escitalopram, bupropion, and buspiron). The purpose of this section is to better characterize the risk of TD with quetiapine in patients with MDD or GAD using data from multiple sources.

A review of quetiapine clinical studies suggests that the risk is low, as supported by the frequency of TD AEs associated with quetiapine across all indications (0.2%, 53/26454 patients in Pool A, all studies). This section reviews the quetiapine clinical study data (Section 4.3.3), postmarketing data (Section 4.3.6), and the peer-reviewed current literature on TD (Section 4.3.7).

### 4.3.2 Background

TD is characterized by repetitive, involuntary, purposeless movements, including chewing, tongue protrusion, vermicular (ie, worm-like) tongue activity, lip smacking, lip puckering, lip pursing, and paroxysms of rapid eye blinking (Casey 1990). Choreoathetoid movements in the limbs and trunk can occur and individuals may rarely experience aerophagia and irregular respiratory rates and may emit grunting noises (Casey 1990).

While there is a paucity of published data describing TD incidence in patients with MDD or GAD, there are some reports in the literature of TD symptoms developing after treatment with tricyclic antidepressants (TCAs), such as imipramine, amitriptyline, doxepin, and clomipramine (Gill et al 1997). Moreover, persistent symptoms of TD lasting for ≥3 months have been reported following discontinuation or dose reduction of the latter three TCAs (Gill et al 1997). A range of dyskinesias have been associated with the use of selective serotonin reuptake inhibitors (SSRIs) (Gill et al 1997).

There are reports in the literature of dyskinesia in patients with schizophrenia that predate the use of conventional antipsychotics (Awouters et al 1990) and of dyskinetic movement

disorders that occur spontaneously in elderly individuals, both healthy subjects and patients with schizophrenia (Latimer 1995, Woerner et al 1991). TD is a dynamic syndrome that can have periods of worsening and remission (Eberhard et al 2006). Up to 60% of patients with TD who have their treatment with a conventional antipsychotic discontinued can be expected to achieve improvement in their TD; however, patients may risk relapse in the absence of medical treatment (Lloyd 1992). The majority of data relate to patients with schizophrenia and related psychoses, and the role of antipsychotics.

Although the potential roles of non-dopaminergic mechanisms have been discussed (Casey 2004, Margolese et al 2005a), there is no consensus on the neuropharmacology underlying the reported lower incidence of TD associated with atypical antipsychotics. The pathophysiology of TD is only partially understood, but sustained blockade of dopamine D2 receptors is generally agreed to be a key-contributing factor (Casey 2004, Margolese et al 2005a). Since occupancy of D2 receptors is dose dependent (Farde et al 1986), both the degree and duration of D2 receptor occupancy is assumed to be related to the long-term risk of TD. This assumption is supported by the demonstration of low (20% to 63%) D2 receptor occupancy in patients treated with clozapine (Nordström et al 1995), a finding that provides a mechanistic explanation for the low risk of TD attributed to clozapine (Kane et al 1993). Consequently, drugs with demonstrated low D2 receptor occupancy at their clinically effective dose range are expected to carry less risk of TD.

The mode of action of quetiapine is relevant when considering risk of TD in this context. Of particular interest are the consistent Positron Emission Tomography (PET) demonstrations of low to moderate (<60%), transient D2 receptor occupancy throughout the clinical dose range. Indeed, patients treated with low doses of quetiapine XR (300 mg/d) had no more than 26.5% (±8.5%) D2 receptor occupancy (Mamo et al 2008). Thus very low D2 receptor occupancy is expected at the dose ranges demonstrated to be effective in the MDD and GAD populations (50 to 300 mg/day). Since sustained high D2 receptor occupancy is a key factor underlying TD (Casey 2004, Margolese et al 2005a), the demonstrated very low occupancy by quetiapine XR provides mechanistic support for a reduced probability of acute TD as compared to antipsychotic treatments.

In schizophrenia, risk factors for TD include advanced age and female gender (Schooler and Kane 1982, Yassa et al 1992). Other potential risk factors include the cumulative antipsychotic exposure and certain forms of extrapyramidal symptoms (EPS), ie, akathisia and parkinsonism (Kane 1999, Kane et al 1984, Miller DD et al 2005). There have also been reports of TD occurring in patients with affective disorders.

### 4.3.3 Incidence of TD in clinical program

To characterise the incidence of TD in quetiapine clinical studies, data were examined for AE reports of tardive dyskinesia (MedDRA preferred term) and dystonia tarda (MedDRA lower level term) (hereafter referred to as TD AEs) for all studies in the quetiapine program. The pooling approach for the clinical study data is described in Section 3.1.

Abnormal Involuntary Movement Scale (AIMS) and EPS data from the quetiapine clinical program are also presented.

#### 4.3.3.1 Incidence of TD adverse events in Pool A (all studies)

Adverse events associated with TD were summarized across Pool A (all studies regardless of indication or study design) to obtain an overall incidence of TD AEs. The incidence of TD AEs in Pool A was 0.20%. Exposure in patient-years and incidence rate per 100 patient-years is summarized in Table 28. As a contrast, the frequency of TD AEs reported during the premarketing evaluation of aripiprazole, the only antipsychotic approved for MDD, is listed in the Abilify label as between 0.10% and 1%.

**Table 28 Incidence of TD adverse events in Pool A (all studies)**

| MedDRA TD term | n | (%) | Exposure[a] | Incidence rate per 100 patient-years[b] |
|---|---|---|---|---|
| Any[c] | 53 | (0.20) | 7862.3 | 0.7 |
| Tardive dyskinesia | 51 | (0.19) | 7864.2 | 0.6 |
| Dystonia tarda[d] | 2 | (0.01) | 7888.1 | 0.0 |

[a] In patient-years, censored at 1st event (ie, exposure no longer calculated for a given patient after the occurrence of the initial AE of interest).
[b] Total number of patients with event x 100/total patient years of censored exposure.
[c] Patients could have more than 1 adverse event, thus, number of patients with any TD event is not necessarily the sum of numbers of patients with individual TD events.
[d] MedDRA lower level term.
TD Tardive dyskinesia.

Of the 53 TD AEs in Pool A, none were reported in MDD and GAD, 42 in schizophrenia, 5 in bipolar disorder and 6 in other indications, mainly dementia related psychosis. Of the 53 cases, 42 were confounded by prior medications and medical history.

Twelve subjects over 60 years of age reported a TD AE, while 41 subjects were 18-60 years of age. Men more commonly reported a TD AE than women. Most TD AE reports were mild-to-moderate in severity; only 1 TD adverse event was reported as serious. Four of the 53 patients discontinued due to 'TD AE'. In about half of the cases, the outcome was reported to be resolved (21 resolved, 25 on-going, 7 unknown).

#### 4.3.3.2 Incidence of TD adverse events in Pool B (placebo-controlled studies)

In Pool B (placebo-controlled studies with quetiapine XR or IR, controlled from study start, any duration of treatment), 8 patients treated with quetiapine and 1 treated with placebo had a TD AE; incidence per 100 patients-years is shown in Table 29.

**Table 29 Incidence of TD adverse events in Pool B (placebo-controlled short-term studies)**

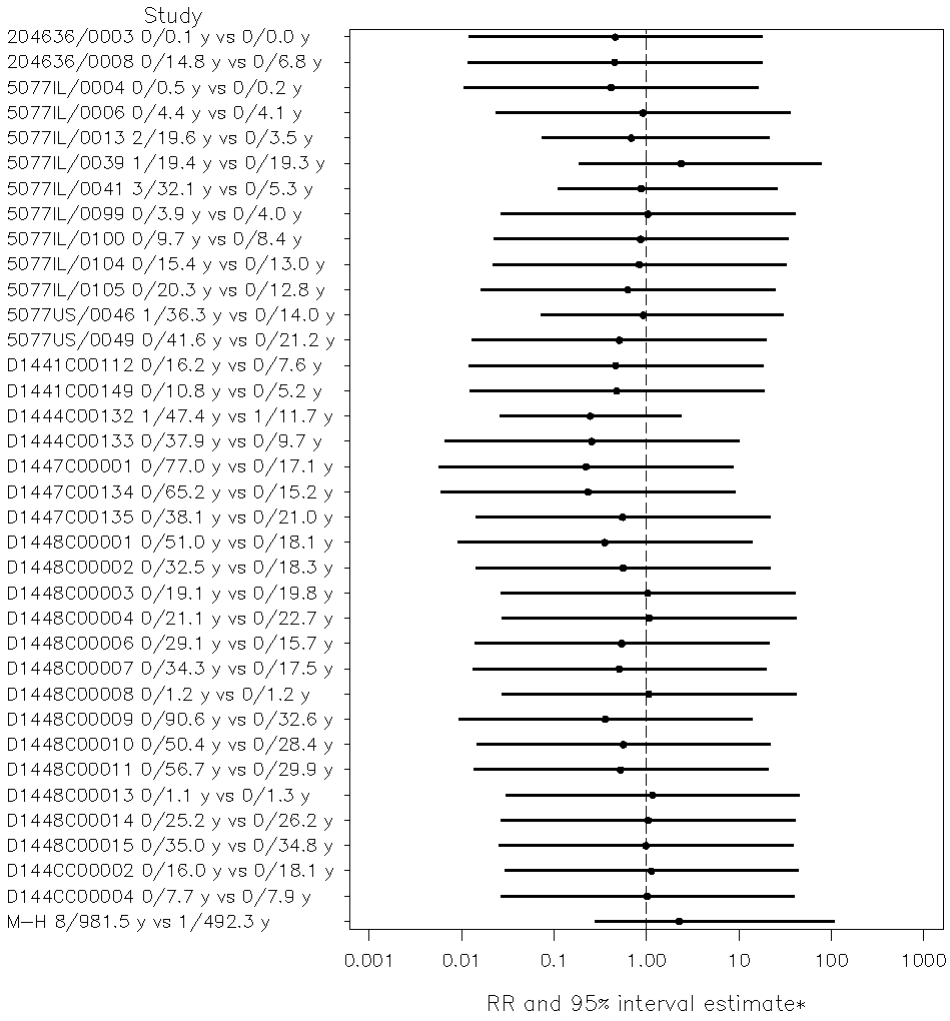
| MedDRA TD term | N[a] | n | Exposure[b] | MH incidence per 100 pt-yrs[c] | MH relative risk[d,g]: QTP vs PLA (95% CI) |
|---|---|---|---|---|---|
| **Tardive dyskinesia/Dystonia tarda[e]** | | | | | |
| Quetiapine | 8853 | 8[f] | 981.5 | 0.6 | 2.26 (0.28, 107.53) |
| Placebo | 4359 | 1 | 492.3 | 0.3 | |

[a] Patients who received at least 1 dose of study medication
[b] In patient-years, censored at first event.
[c] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[d] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
[e] MedDRA lower level term.
[f] Of these patients, 7 had schizophrenia and 1 had dementia-related psychosis.
[g] RR estimate and CI calculated using Exact methods

Of the 8 TD AEs on quetiapine in Pool B, 7 were in schizophrenia and 1 in dementia related psychosis. The case on placebo was a schizophrenia patient. It should be noted that, of the 35 studies in Pool B, 30 studies had no event on either quetiapine or placebo treatment and thus these studies do not contribute to the estimate of relative risk shown in Table 29. Of the contributing 5 studies with at least one event, the placebo event rate arises from 1 event in 1 study. The consequence of this pattern of data is the relative risk may be somewhat over estimated. Nevertheless, and notwithstanding the possibility of some inflation of the relative risk estimate, the relative risk for TD AEs in placebo-controlled studies across all indications was associated with a wide CI consistent, with both a large increase and a large decrease in the risk of an event with quetiapine treatment compared to placebo. This can also be seen in Figure 9 which shows no consistent pattern toward and increase risk of TD with quetiapine treatment across studies.

Figure 9 presents relative risk estimates for tardive dyskinesia related adverse events in all placebo-controlled studies (Pool B).

**Figure 9 Forest plot of tardive dyskinesia related adverse events in Pool B (all placebo-controlled studies)**




* Exact MH confidence interval. Individual study data are 95% credibility intervals

#### 4.3.3.3 Incidence of TD adverse events in Pool C (all long-term randomized withdrawal studies)

In Pool C (long-term randomized withdrawal studies quetiapine exposure across indications, 1025.5 / 704.1 patient years for quetiapine/placebo), there was 1 patient in the placebo group and 1 patient in the quetiapine group (400 mg) with TD. The incidence per 100 patient years was 0.1% in each group and the relative risk was 0.61 (0.04, 9.85).

#### 4.3.3.4 Incidence of TD adverse events in Pool D (all MDD and GAD studies)

In Pool D (all studies in the MDD and GAD program), patients were exposed to a lower dose range (50 to 300 mg) than in schizophrenia and bipolar disorder studies. Overall exposure in

Pool D was 1404.8 patient-years in 6,816 patients that received quetiapine XR. Of these patients, 519 received quetiapine XR for at least 6 months and 123 for at least 12 months.

There were no reports of TD AEs in any patient in Pool D (the MDD and GAD programs).

### 4.3.4 AIMS data: incidence of TD per Schooler-Kane criteria

In order to further characterize the risk of quetiapine treatment on the incidence of TD in Pool D (the MDD and GAD programs), AstraZeneca examined Abnormal Involuntary Movement Scale (AIMS). The AIMS was developed by the National Institute of Mental Health for use in evaluating the presence and severity of abnormal movements (Guy 1976). The AIMS was originally developed as a research tool, but is occasionally utilized by clinicians as a tool for examining dyskinesia in clinical practice (Munetz and Benjamin 1988). The AIMS was prospectively performed in the long-term MDD and GAD studies. In order to gain consistency in defining movements as tardive dyskinesia, a retrospective analysis of the AIMS data using the Schooler Kane (Schooler and Kane 1982) criteria was conducted. In evaluating the AIMS data after application of the Schooler Kane criteria, some movements that may not have been identified as TD by the clinician or the patient, may be identified as presumptive TD based upon the specified research criteria. See Appendix C1 for a description of the Schooler Kane criteria.

In Pool D (all MDD and GAD studies) population, the incidence of patients meeting the criteria was 0.21% for the longer-term studies, and 0.26% for the studies in elderly patients (see Table 50 in Appendix C1). In randomized withdrawal studies in bipolar disorder, the incidence of TD per Schooler-Kane criteria was 0.58%. In the long-term schizophrenia studies examined, the incidence of TD per Schooler-Kane was 2.4%.

### 4.3.5 EPS adverse events

While there are reports that suggest a significant association between EPS and TD risk, they emphasize that EPS manifestations do not robustly identify individuals with a high risk for TD (Tenback et al 2006). There is thus insufficient evidence to substantiate the use of EPS as a surrogate marker for TD liability.

However, the EPS profile of antipsychotics may yet have some broad utility in determining the general level of TD risk that might be anticipated. Therefore, AstraZeneca also examined the incidence of aggregated EPS adverse events (EPS-related AEs) across indications to further characterize the potential risk of TD with quetiapine treatment.

The frequency of EPS-related AEs reported in Pool A, all studies across all indications, was slightly higher with quetiapine XR compared to placebo (7.1% vs 5.2% respectively).

In the 4 short-term MDD or GAD studies that included active controls (duloxetine, paroxetine, and escitalopram), the incidence of EPS-related AEs with quetiapine (6.1%, across doses) was lower than that seen with any of the active controls (7.4% to 9.4%). The difference was primarily attributed to the greater incidences of tremor and/or restlessness seen with the active

controls. In these studies, the incidence of EPS-related AEs with any active treatment was greater than the incidence seen with placebo (3.6%).

### 4.3.6 Postmarketing data

A review of the AstraZeneca internal postmarketing database was undertaken using a search strategy that included the MedDRA preferred term of tardive dyskinesia and the MedDRA lower level term of tarda dystonia (ie, tardive dystonia). Among the more than 22 million patients with known exposure to quetiapine (XR or IR), 689 cases matched the search criteria employed. Most cases were confounded by concomitant or prior medication, comorbid risk factors and/or an alternative cause, or contained incomplete information regarding medical history, concomitant drugs and/or course, treatment or outcome of the events of TD, and the relationships of these events to quetiapine or quetiapine XR.

### 4.3.7 Literature review

A comprehensive literature search was undertaken to examine frequency of TD with drug use, frequency of TD in certain disease states, and possible risk factors for TD. The majority of data on TD comes from populations with psychotic disorders, which have a relatively high frequency of this disorder.

Although the literature differs regarding the comparative frequency of TD associated with atypical antipsychotics and other, older first-generation neuroleptics, the sum total of the evidence to date clearly suggests that TD is more commonly associated with these older neuroleptics (ie, and less common with the atypical antipsychotics). Of particular note are two systematic reviews describing 23 clinical studies lasting ≥1 year in pediatric, adult and elderly patients (n=30,820) who had received treatment with antipsychotics, which concluded that the overall risk for TD was lower in atypicals compared with conventional antipsychotics (Correll and Schenk 2008; Correll et al 2004).

The first review of 11 studies (n=2,769; mean age, 45.4 years; male, 60.8%; White, 85.8%) was primarily in patients with schizophrenia, schizophreniform disorder and schizoaffective disorder (82.1%) or dementia (11.2%) and reported that the overall weighted mean annual incidence rate of TD associated with atypicals (quetiapine, amisulpride, olanzapine, risperidone, and ziprasidone) was 2.1% compared with 5.4% in adults treated with haloperidol. A subsequent update to the original review focusing on 12 studies published from 2005 onwards, primarily in patients with dementia and mixed diagnoses (78.7%) or schizophrenia (19.2%) (n=28,051; mean age, 39.7 years; male, 59.7%; White, 70.9%) reported a significant difference in annualized TD incidences between antipsychotic classes (3.95% and 5.5% in patients treated with atypical and conventional antipsychotics, respectively; $p<0.0001$).

In a 12-month follow-up of the Intercontinental Schizophrenia Outpatient Health Outcomes (SOHO) study, the incidence of TD was 5.0%, 7.3%, 11.4% and 19.6% in patients treated with olanzapine, quetiapine, risperidone and haloperidol, respectively (Dossenbach et al 2005). Odds ratios (OR) for developing a TD adverse event versus olanzapine were:

quetiapine, 1.45 (95%CI: 0.48–4.34); risperidone, 3.04 (95%CI: 2.00–4.63); haloperidol, 10.50 (95%CI: 5.61–19.67).

Not all publications have reported the aforementioned clinically meaningful class-based differences in TD risk between atypical and conventional antipsychotics (Chakos et al 2001, de Leon 2007, Miller DD et al 2008). The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study in 1493 patients with schizophrenia identified no statistically significant differences between treatments groups in any measure of TD (eg, covariate-adjusted 12-month TD event rates were 0.7% to 2.2% in the atypicals compared with 2.7% in the perphenazine-treated cohort, Miller DD et al 2008). Potential limitations of this study include limited exposure to antipsychotics during Phase 1 (3.5 to 9.2 months), very long history of antipsychotic exposure proceeding phase 1, possible unmasking of TD due to prior antipsychotic therapy, and the exclusion of patients with TD from randomization to the perphenazine group (Miller DD et al 2008, Swartz et al 2008).

### 4.3.8 Conclusions on tardive dyskinesia

- ***While there exists a risk of TD with quetiapine, as indicated in the product labeling, this risk is low, as supported by the frequency of TD AEs associated with quetiapine in clinical studies across all indications (0.2%, 53/26454 patients).*** Results suggest that the risk of TD may be lower in the MDD and GAD populations than in schizophrenia and bipolar patients treated with quetiapine.

## 4.4 Sudden cardiac death

### 4.4.1 Introduction

A recent publication in the New England Journal of Medicine (Ray et al 2009) evaluated the risk of sudden death in patients using typical and atypical antipsychotic drugs. This has prompted AstraZeneca to conduct an evaluation of currently available data for quetiapine as part of the ongoing pharmacovigilance process. Additionally, the Division has asked AstraZeneca to comment on the topic of sudden death in the context of patients with MDD and GAD.

In order to address this issue, the sections that follow will review the article by Ray et al 2009, and present safety data on sudden death and related AEs of interest from the quetiapine clinical development program and post-marketing database, and a review of pertinent QT data for quetiapine.

### 4.4.2 Background

Sudden cardiac death (SCD) is an unexpected, pulseless condition from a cardiac cause (Chugh et al 2008). A well-accepted case definition is unexpected death occurring within 1 hour of symptom onset in the absence of a prior condition that would appear fatal. If unwitnessed the person should have been seen alive within 24 hours prior to death (Myerburg and Castellanos 2009). Understanding the population burden of and risk factors for SCD is complicated by its unpredictable occurrence, the inconsistent use of standard case definitions, difficulty in excluding non-cardiac causes such as pulmonary embolism, and differences in

study design. For example, retrospective assessment of cases, based on death certificates, may overestimate cases by as much as 200% to 300%. Prospective, community-wide studies, using multiple sources of ascertainment appear to provide the most accurate estimates (Chugh et al 2008).

Ventricular tachyarrhythmia is often the proximate cause of SCD (Anderson 2008) with at least 80% of cases of SCD occurring in patients with significant coronary artery disease, either symptomatic or previously silent (Kannel et al 1990, Myerburg et al 1997). The relationship between SCD and coronary artery disease is reflected in the epidemiology of SCD: male gender, smoking, obesity, diabetes, and inactivity are all associated with increased SCD risk (Zipes and Wellens 1998). The Rotterdam Study, a population-based prospective cohort study, provides strong evidence that QTc prolongation is an independent risk factor for sudden cardiac death (adjusted Hazard Ratio: 2.5, 95% CI: 1.3 - 4.7) after adjustment for age, gender, body mass index, hypertension, lipids, diabetes mellitus, myocardial infarction, heart failure, and heart rate (Straus et al 2006).

Most recently, the Oregon Sudden Unexpected Death Study evaluated determinants of prolonged QTc and the relationship of prolonged QTc to SCD risk in patients with coronary artery disease. QTc prolongation of unknown origin (Chugh et al 2009) was an even stronger predictor of SCD. However, diabetes mellitus and the use of QT prolonging drugs were also significant predictors of SCD.

Patients with depression also have an increased risk for SCD. One study using a retrospective database analysis found a hazard ratio of 2.74 (95% confidence interval [CI] 1.37-5.50) for SCD among patients with depressive symptoms compared to non-depressed controls (Luukinen et al 2003). Depression may be associated with increased risk for SCD and cardiovascular disease because it is associated with physiological changes that negatively influence the cardiovascular system, including nervous system activation, cardiac rhythm disturbances, systemic and localized inflammation, and hypercoagulability (Joynt et al 2003).

Additionally, after adjusting for other clinical and demographic factors, phobic anxiety and depression have each been associated with ventricular arrhythmia (Straus et al 2006**,** Watkins et al 2006).

The cardiovascular toxicity of the older generation of tricyclic antidepressants is well established (American Psychiatric Association 2000, Pacher and Kecskemeti 2004). In addition, an increasing number of case reports have demonstrated that the use of SSRIs is associated with cases of arrhythmias, prolonged QTc interval and orthostatic hypotension in patients lacking cardiovascular disorder (Pacher and Kecskemeti 2004).

### 4.4.3 Risk of sudden death in patients using typical and atypical antipsychotic drugs

In a study using a retrospective analysis of a Medicaid database, Ray et al 2009 calculated the incidence of SCD among current users of single typical antipsychotic drugs (n=46089), single atypical antipsychotic drugs (n=44218), and 186600 matched nonusers of antipsychotic drugs regardless of diagnosis. The authors reported that current users of typical and atypical

antipsychotic drugs had higher rates of SCD than did nonusers; the incidence rate ratios (IRRs) were 1.99 (95% CI 1.68-2.34) and 2.26 (95% CI 1.88-2.72) respectively. Risk increased with increasing dose in both groups, and no statistically significant difference in rate between typical and atypical antipsychotic drug users was observed.

Quetiapine was one of 4 atypical antipsychotics considered. There were 40 cases of SCD in 17355 patient-years of exposure to quetiapine. The IRR for current users of quetiapine compared to nonusers of antipsychotics was 1.88 (95% CI 1.30-2.71), with a numeric, but not statistically significant, dose-dependent relationship. For quetiapine, there were 3, 15, and 22 deaths in the low, moderate, and high dose categories, respectively, corresponding to a quetiapine dose of approximately <75, 75-224, and >224 mg. The corresponding IRRs were 1.09 (95% CI 0.3-3.4) (low dose), 1.62 (95% CI 1.0-2.7) (moderate dose), and 2.85 (95% CI 1.8-4.4) (high dose). Use of other individual agents, compared to non-users of antipsychotics, was associated with IRRs of 3.67 (95% CI 1.94-6.94) for clozapine, 2.91 (95% CI 2.26-3.76) for risperidone, and 2.04 (95% CI 1.52-2.74) for olanzapine. When adjusting for propensity scoring, the IRR was 8.08 (95% CI 2.58-25.23) for clozapine, 1.49 (95% CI 0.98-2.27) for quetiapine, 2.49 (95% CI 1.72-3.62) for risperidone, and 1.99 (95% CI 1.41-2.79) for olanzapine.

As the authors acknowledge, the primary limitation of the study is the existence of potential confounding factors associated with the use of antipsychotic drugs. These include cardiovascular and other somatic diseases, concurrent use of other proarrhythmic medications, mood disorders, and behavioral risk factors such as substance abuse, poor self-care, and smoking. Although the authors of this study attempted to manage the effect of confounding factors through study design elements, secondary analyses, and sensitivity analyses (including stratification, restriction, and propensity score matching), they point out that residual effects on the data cannot be entirely ruled out.

Several additional epidemiologic studies have assessed the risk of SCD among patients taking antipsychotic medications. In a Netherlands-based study, which did not include quetiapine, current use of antipsychotics was associated with a 3-fold increase in risk of SCD (odds ratio 3.3 [95% CI 1.8-6.2], Straus et al 2004).

Hennessey et al found that clozapine, haloperidol, risperidone, and thioridazine were significantly associated with increased risk for cardiac arrest, ventricular arrhythmia, and death (Hennessey et al 2002). A 2001 study in the Tennessee Medicaid database found the increasing exposure to conventional (typical) antipsychotics was associated with increasing risk for SCD compared to nonuse of these agents (Ray et al 2001).

### 4.4.4 Safety data from quetiapine development program

#### 4.4.4.1 Data sources and pooling

For analyses of mortality and adverse events (AEs) from clinical studies, all short and long-term, controlled and uncontrolled studies across all indications and formulations in the quetiapine clinical safety database are included, based on the pools described in Section 4.1.

Included in this section are:

- Analyses of reports of death, including
  - Analyses of all-cause mortality
  - Analyses of reports with investigator-reported terms that may potentially indicate SCD
  - A post-hoc blinded adjudication of reports performed by an external cardiologist reviewer
- Analyses of reports containing terms that may be suggestive of serious ventricular arrhythmia (including torsades de pointes) and QT prolongation.

### 4.4.5 Sudden cardiac death in quetiapine clinical studies

In clinical studies involving quetiapine, AEs were not prospectively adjudicated but were mapped to preferred terms (PTs) based on events as reported by the Investigator. Therefore, several different strategies were employed to identify reports in clinical studies describing events potentially resulting in SCD due to a fatal ventricular tachyarrhythmia (FDA ICH E14 Guidance 2005, Ray et al 2009):

- An analysis of "all cause mortality" in clinical studies involving quetiapine was performed, identified from both the clinical study database and AstraZeneca's global safety database. Reports of death that were identified after a study terminated may only have been captured in the latter, so both databases were searched to ensure no cases of death were missed.
- A search was performed to identify reports in the clinical study database describing events mapping to PTs that may suggest sudden cardiac death resulting from a fatal ventricular tachyarrhythmia. The terms used were "sudden death", "sudden cardiac death", "cardiac death" "cardiac arrest", and "cardio-respiratory arrest. Additional cases found in the AstraZeneca's global safety database are included in this analysis.
- Reports of death (excluding homicides, completed suicides not involving an overdose with quetiapine, and accidental injuries) from the clinical study database as well as additional cases identified in the AstraZeneca global safety database with PTs that potentially describe events related to SCD were reviewed by a blinded external expert consultant who classified reports as either sudden cardiac death, insufficient information, or not a case of sudden cardiac death, using the criteria described by Ray et al 2009: "A sudden pulseless condition that was fatal, that was consistent with a ventricular tachyarrhythmia, and that occurred in the absence of a known noncardiac condition as the proximate cause of death."

The findings of these 3 sets of analyses are described in the following sections.

### 4.4.6 Mortality from all causes in clinical studies

Adverse events in the clinical study program were investigator reported and not adjudicated during the time of the studies. To characterize the overall risk of death on quetiapine, mortality from all causes was evaluated. "Mortality from all causes" includes all patients who were reported to have a fatal outcome, regardless of cause.

Table 30 presents the data in all study pools, across all indications.

**Table 30 Mortality from all causes in all pools (Mantel-Haenszel)**

| Treatment | Patients with event | Total patients[a] | Exposure[b] | Incidence rate per 100 pt-yrs[c] | MH incidence rate per 100 pt-yrs[d] | MH relative risk[e] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|
| Pool A (all studies) | | | | | | | | |
| QTP | 119 | 26454 | 7890 | 1.51 | | | | |
| Placebo | 18 | 6375 | 1196.7 | 1.50 | | | | |
| Comparator | 19 | 4001 | 787.4 | 2.41 | | | | |
| Pool B (Placebo-controlled short-term studies) | | | | | | | | |
| QTP | 24 | 8853 | 981.7 | | 2.5 | 1.08 | 0.53 | 2.20 |
| Placebo | 12 | 4359 | 492.4 | | 2.3 | | | |
| Pool C (All long-term randomized withdrawal studies) | | | | | | | | |
| QTP | 2 | 2043 | 1026.0 | | 0.20 | 0.24 | 0.05 | 1.16 |
| Placebo | 6 | 2016 | 704.3 | | 0.85 | | | |
| Pool D (All MDD and GAD studies) | | | | | | | | |
| QTP | 5 | 6816 | 1404.8 | 0.36 | | | | |
| Placebo | 2 | 2622 | 437.6 | 0.46 | | | | |
| Comparator | 0 | 730 | 93.5 | 0.0 | | | | |
| Pool E (Long-term MDD and GAD randomized withdrawal studies) | | | | | | | | |
| QTP | 0 | 607 | 242.0 | | 0.00 | 0.00[f] | 0.00[f] | 29.04[f] |
| Placebo | 1 | 601 | 173.7 | | 0.57 | | | |

[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years.
[c] 100 x total number of patients with event/total patient years of exposure.
[d] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[e] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
[f] RR estimate and CI calculated using Exact methods.

Note: Based on the variable adverse-event-outcome in the clinical safety database and the global safety database.

Across these data pools there is no evidence of an increase in the risk of death with quetiapine treatment relative to placebo. The relative risk or incidence rate per 100 patient years for death was at least similar for quetiapine versus placebo overall and across the indications of schizophrenia, bipolar disorder, MDD and GAD. Table 31 presents mortality from all causes from Pool A (all studies).

**Table 31 Mortality from all causes in Pool A (all studies) by indication**

| Treatment | Patients with event | Total patients[a] | Exposure[b] | Incidence rate per 100 patient-years [c] |
|---|---|---|---|---|
| All Indications | | | | |
| Quetiapine | 119 | 26454 | 7890.0 | 1.51 |
| Placebo | 18 | 6375 | 1196.7 | 1.50 |
| Comparator | 19 | 4001 | 787.4 | 2.41 |
| Schizophrenia | | | | |
| Quetiapine | 36 | 9450 | 3119.6 | 1.15 |
| Placebo | 1 | 702 | 66.7 | 1.50 |
| Comparator | 9 | 2245 | 448.3 | 2.01 |
| Bipolar disorder | | | | |
| Quetiapine | 13 | 8830 | 2937.2 | 0.44 |
| Placebo | 7 | 2706 | 656.6 | 1.07 |
| Comparator | 0 | 842 | 221.1 | 0.00 |
| MDD and GAD | | | | |
| Quetiapine | 5 | 6816 | 1404. 8 | 0.36 |
| Placebo | 2 | 2622 | 437. 6 | 0.46 |
| Comparator | 0 | 730 | 93.5 | 0.00 |
| Other | | | | |
| Quetiapine | 65 | 1357 | 428.4 | 15.17 |
| Placebo | 8 | 345 | 35.8 | 22.35 |
| Comparator | 10 | 184 | 24.5 | 40.82 |

[a] Patients must have received at least 1 dose of study medication.
[b] Exposure in patient-years.
[c] Values are 100 times the total number of patients with event/total number of patients.
Note: Based on the variable adverse-event-outcome in the safety database and the global safety database.

Of the 119 quetiapine patients who died across all studies, 65 were enrolled in studies for elderly patients with dementia and/or psychosis. There were no deaths in the Phase I program.

Overall, across all studies, the incidence density of deaths for patients treated with quetiapine versus placebo was similar. There is no apparent difference in all cause mortality by indication or by gender. The incidence density across all indications (including the dementia studies) was similar for quetiapine and placebo for patients 18 to 39, 40 to 64 years of age, and > 74 years of age; however, for patients 65 to 74, the incidence density was higher for quetiapine compared with placebo (5.95 versus 1.5).

The majority of the 119 patient deaths on quetiapine were due to respiratory events (28) and cardiovascular events (29) (as reported by the Investigator using standard Medical Dictionary for Regulatory Activities [MedDRA] terms). The other deaths were attributed to infection, suicide, other, and cause of death unknown (8 each); accidental death, cancer (7 each); and cerebral vascular accident (6). There were 4 deaths from overdose and 3 deaths each from the causes of renal failure, and gastrointestinal related. Ten of the quetiapine deaths, but none of the deaths for placebo or active comparator, occurred more than 30 days after the patient was off treatment.

#### 4.4.6.1 Sudden cardiac death in quetiapine clinical studies

As described in Section 4.4.5, a search was performed to identify reports in the clinical study database describing events mapping to PTs that may suggest SCD. The terms chosen were "sudden death", "sudden cardiac death", "cardiac death" "cardiac arrest", and "cardio-respiratory arrest". Additional cases found in the AstraZeneca's global safety database with these PTs are included in this analysis.

Sixteen reports of sudden death in patients receiving quetiapine, with 7980 patient-year exposure, were identified in the clinical studies database or global safety database. There were 0 cases (1197 patient-years exposure) reported in the placebo group, and 2 (787 patient-years exposure) reported for the comparator group.

#### 4.4.6.2 External review of mortality data

In the clinical studies, cases resulting in death were not prospectively adjudicated; rather, AEs resulting in death were mapped to PTs based on events as reported by the Investigator. Therefore, it is possible that not all cases of sudden death are captured by the PT terms related to SCD described in Section 4.4.5.

To provide a more robust analysis of sudden death, a cardiologist external to AstraZeneca was asked to review reports of death in a blinded fashion from the clinical study database (excluding homicides and non-overdose suicides), plus additional cases found in the AstraZeneca global safety database with PTs of sudden death (see Section 4.4.5).

Seventeen additional cases of death in the global safety database, with causes of death as reported by the Investigator that did not map to PTs that may suggest sudden cardiac death resulting from a fatal ventricular tachyarrhythmia (eg respiratory events, cancer, suicide, etc.), are currently being adjudicated. Of these seventeen cases, 11 were on quetiapine, 2 on placebo, and 4 on comparator. These reports are described in Table 53 in Appendix D, and are further discussed below.

Cases were adjudicated as meeting or not meeting the case definition for sudden death utilized by Ray et al (see Section 4.4.5).

**Table 32 Sudden death in all pools, based on adjudicated cases**

| Treatment | Patients with event | Total patients[a] | Exposure[b] | Incidence rate per 100 pt-yrs[c] | MH incidence rate per 100 pt-yrs[d] | Relative risk[f] QTP vsPla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|
| Pool A (all studies) | | | | | | | | |
| QTP | 23 | 26454 | 7890 | 0.29 | | | | |
| Placebo | 8 | 6375 | 1196.7 | 0.67 | | | | |
| Comparator | 4 | 4001 | 787.4 | 0.51 | | | | |
| Pool B (Placebo-controlled short-term studies) | | | | | | | | |
| QTP | 4 | 8853 | 981.7 | | 0.36 | 0.46 | 0.09 | 2.24 |
| Placebo | 5 | 4359 | 492.4 | | 0.88 | | | |
| Pool C (All long-term randomized withdrawal studies) | | | | | | | | |
| QTP | 0 | 2043 | 1026.0 | | 0.00 | 0.00 | 0.00 | 1.77 |
| Placebo | 3 | 2016 | 704.3 | | 0.42 | | | |
| Pool D (All MDD and GAD studies) | | | | | | | | |
| QTP | 3 | 6816 | 1404.8 | 0.21 | | | | |
| Placebo | 1 | 2622 | 437.6 | 0.23 | | | | |
| Comparator | 0 | 730 | 93.5 | 0.0 | | | | |
| Pool E (Long-term MDD and GAD randomized withdrawal studies) | | | | | | | | |
| QTP | 0 | 607 | 242.0 | | 0.00 | 0.00 | 0.00 | 29.04 |
| Placebo | 1 | 601 | 173.7 | | 0.57 | | | |

[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years.
[c] 100 x total number of patients with event/total patient years of exposure.
[d] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[e] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
[f] RR estimate and CI calculated using Exact methods
Note: Based on the variable adverse-event-outcome in the clinical safety database and the global safety database.

Analysis of the adjudicated cases shows no evidence of an increase in the risk of sudden death with quetiapine treatment relative to placebo. The relative risk or incidence density of sudden cardiac death was at least similar to quetiapine and placebo across all pools.

Of the 123 reports provided to the cardiologist for blinded adjudication, 23 quetiapine reports were adjudicated as sudden death, 64 were adjudicated as not sudden death, and 10 reports were assessed as having insufficient information. For the 13 placebo reports, the

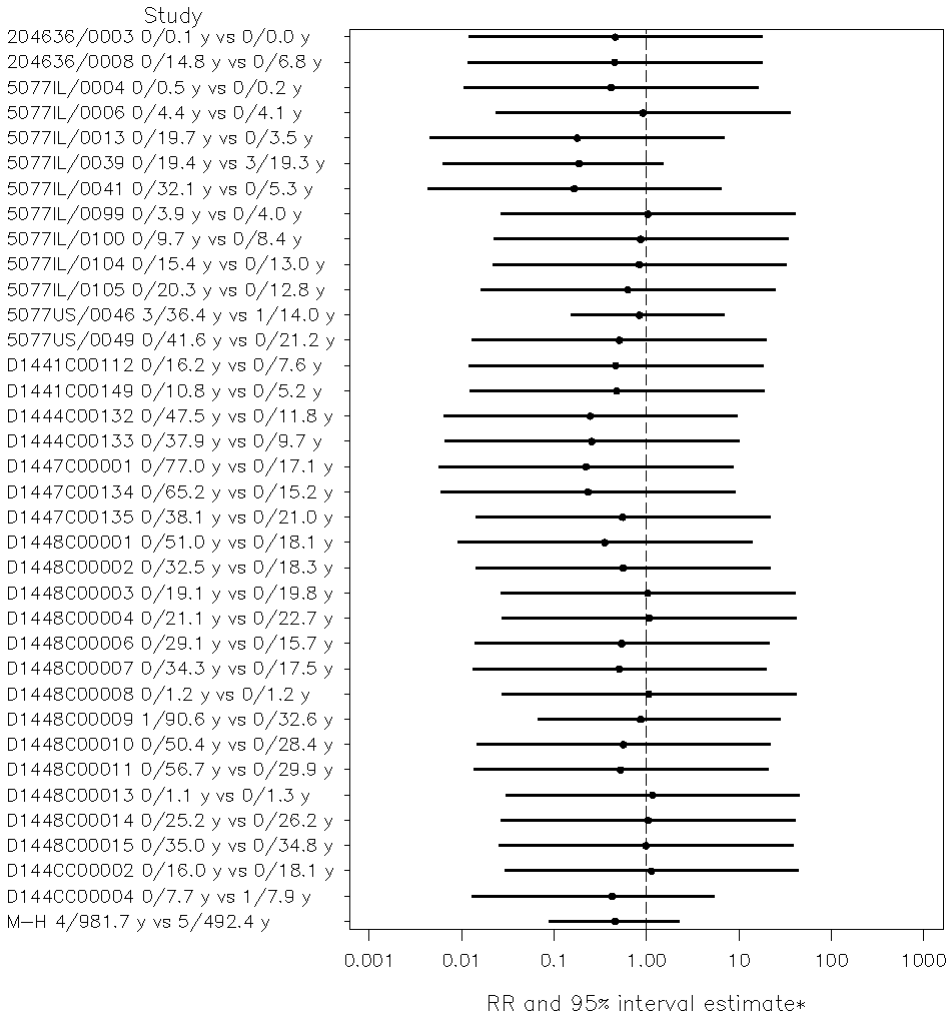
corresponding adjudication numbers were 8, 4, and 1, and for the 13 active comparators, 4, 7, and 2 (sudden death, not sudden death, insufficient information, respectively).

Nine of the 23 reports involving patients treated with quetiapine described patients enrolled in elderly patients with dementia (including Alzheimer's type), which is not an approved indication for quetiapine (Table 51 in Appendix D). These patients had complicated medical histories with multiple comorbidities that may have independently increased the risk of sudden death. It should be noted that the United States (US) label contains a boxed class warning stating that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death (see Appendix E).

The remaining 14 reports involving patients treated with quetiapine were from the indications of schizophrenia (5), bipolar (4), MDD (2), and GAD (1), psychosis (2) (Table 51 in Appendix D). In the majority of these cases, there were potential confounding factors including pre-existing cardiovascular disease. Two cases reported on quetiapine occurred in patients whose last dose of drug was >30 days prior to death.

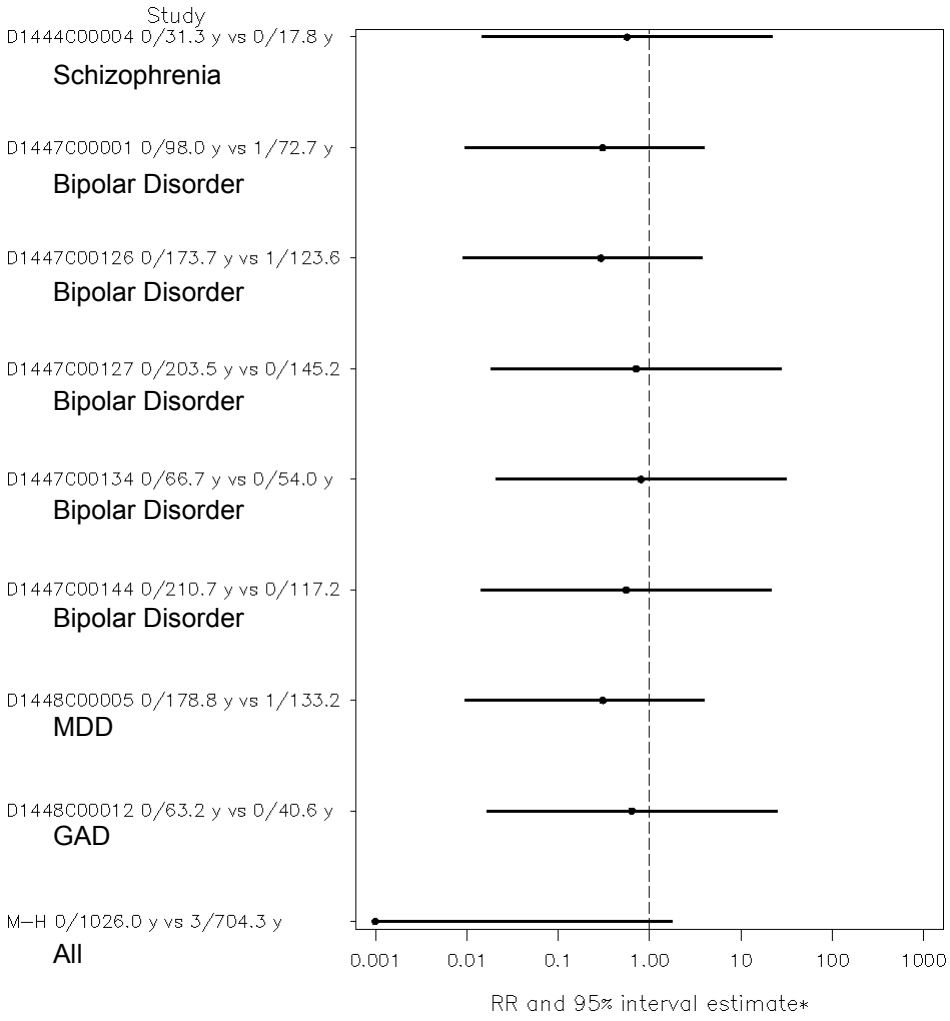
Forest plots of sudden death by study from the adjudicated analysis for Pool B (placebo-controlled studies) and for Pool C (all long-term randomized withdrawal studies), are presented in Figure 10 and Figure 11, respectively.

**Figure 10 Forest plot of sudden death in Pool B (placebo-controlled short-term studies)**




Individual study data are 95% credibility intervals. Exact M-H RR estimate analysis: 0.46 (95% CI: 0.09-2.24)

**Figure 11 Forest plot of sudden death in Pool C (all long-term randomized withdrawal studies)**




Individual study data are 95% credibility intervals. Exact MH RR estimate: 0.00 (95% CI: 0.00, 1.77)

Figure 10 and Figure 11 show no consistent pattern toward an increase risk of sudden death with quetiapine treatment across either short-term studies (Figure 10) or long-term randomized withdrawal studies (Figure 11).

Review of the details of all adjudicated reports of sudden death, and the additional cases pending adjudication, do not identify a higher risk for sudden cardiac death among the patients who were treated with quetiapine. Furthermore, in the unlikely event that the additional cases for quetiapine are adjudicated as sudden death, the overall conclusions from the analyses presented above would not change.

### 4.4.7 QT-related safety data

#### 4.4.7.1 Background

The QT interval comprises the time from the beginning of the QRS complex to the end of the T wave on an ECG, and is measured in milliseconds. The QT interval reflects ventricular depolarization and repolarization and, when prolonged, may predispose an individual to ventricular tachyarrhythmias, which may be fatal. Torsade de pointes is a particular form of polymorphic ventricular tachycardia, potentially leading to ventricular fibrillation and sudden death, that occurs specifically in patients with long-QT syndrome and in patients with drug-induced prolongation of the QT interval (Roden 2004, Roden 2008). Although QT interval prolongation is an imperfect surrogate, in general there is a qualitative relationship between QT prolongation and the propensity to develop torsade de pointes (Roden 2004, FDA ICH E14 Guidance 2005).

Drugs associated with a prolongation of the QT interval corrected for heart rate (QTc) (Roden 2004) include certain anti-arrhythmics, antihistamines, antimicrobials, calcium channel antagonists, tricyclic antidepressants, antipsychotics, and lithium (Roden 2004). Prolongation of the QTc interval is now routinely used in clinical practice and in drug development as a marker of potential risk for the development of polymorphic ventricular tachycardia and torsade de pointes (Roden 2004, FDA ICH E14 Guidance 2005).

A comprehensive review of QT-related data for quetiapine was submitted to the FDA on 26 February 2001, and subsequently reviewed by the Division. Included were reviews of preclinical data, relevant clinical pharmacology studies, and findings from the clinical studies safety database and post-marketing safety reports. After their review of this information, the FDA did not recommend any labeling changes for quetiapine with regards to QT effects. However, as QT interval has been associated with sudden death, an updated analysis of the pertinent clinical study data for quetiapine has been conducted for completeness.

#### 4.4.7.2 Summary of preclinical data

Quetiapine and its metabolites have the potential to inhibit several cardiac ion channels at high concentrations that are unlikely to be achieved in humans. In vitro studies indicate that quetiapine and norquetiapine do not prolong cardiac action potentials. The weight of evidence from in vivo preclinical safety studies indicates that although quetiapine and its metabolites can reduce blood pressure and increase heart rate in animals, QTc intervals are not likely to be affected when quetiapine is used according to the prescribing information.

#### 4.4.7.3 Comparison between quetiapine formulations

A number of biopharmaceutics studies were conducted to evaluate the pharmacokinetic profile of quetiapine XR. Based on pharmacokinetic properties, the effects of quetiapine XR on the QT interval are expected to be similar to the IR formulation.

#### 4.4.7.4 Safety data from the clinical development program

In the sections that follow, QT data from Phase I studies using quetiapine, and the Phase II, III, IV clinical development program for quetiapine are presented.

### Safety data from Phase I studies, including Pfizer Study 54

### AstraZeneca Study 5077IL/0093

AstraZeneca Study 5077IL/0093 was designed to prospectively evaluate the relationship between quetiapine and the QT interval. The findings from study 5077IL/0093 (as well as findings from AstraZeneca Phase I studies that were not designed to prospectively evaluate this question) were inconclusive, neither establishing nor excluding a risk for QT prolongation with quetiapine. However a study performed by Pfizer, Study 54, prospectively evaluated the relationship between several antipsychotics (including quetiapine) on the QT interval and is described below.

### Pfizer Study 54

At an FDA advisory committee held on 19 July 2000, Pfizer presented the results of a prospective study of the effects of their new antipsychotic drug, ziprasidone, on the QT interval, as well as the effects of 5 other antipsychotic drugs including quetiapine (Gordon 2000, Harrigan et al 2004).

This study, performed by Pfizer and designed with FDA input, examined the effects of ziprasidone as well as haloperidol, thioridazine, olanzapine, risperidone, and quetiapine. Haloperidol was not expected to increase the QTc interval, but there was no placebo control. The study also included a phase in which a metabolic inhibitor was added to each drug to determine additive effects on the QTc interval under conditions of maximum inhibition of clearance. The details of this study are described in Appendix D2.

In this prospective, comparative study, the effects of quetiapine were studied over a range of individual plasma concentrations that varied by 2 orders of magnitude, from approximately $10^2$ ng/mL to approximately $10^4$ ng/mL (Gordon 2000). All the correction formulas applied to the data, with the exception of the Bazett formula (known to overestimate the QTc interval when the heart rate is increased), confirmed that the change in QTc interval during quetiapine treatment was no greater than the change during haloperidol treatment.

In Pfizer Study 54, quetiapine 750 mg/day was administered to steady state alone and in the presence of a cytochrome P450 3A4 inhibitor. Mean $C_{max}$ plasma concentrations were1280 ng/mL (61% coefficient of variation) and 3740 ng/mL (43%) in the absence and presence of the cytochrome P450 3A4 inhibitor. In the AstraZeneca development program for quetiapine XR, the mean quetiapine $C_{max}$ for a 300 mg dose of quetiapine XR at steady state was 470 (33% coefficient of variation) ng/mL. Therefore, the mean $C_{max}$ seen in Study 54 is approximately a 2.7 fold multiple (1280 mg/mL versus 470 ng/mL) compared to 300 mg quetiapine XR.

### QT data from quetiapine clinical studies with centrally read ECGs

As of 2001, all multicenter studies included in the quetiapine XR submissions for schizophrenia, bipolar depression, bipolar maintenance, and pediatric patients, as well as other non submission multicenter studies (such as dementia studies including Alzheimer's type dementia) used a central ECG laboratory as the vendor for the central reading and reporting of

ECG tracings including digital ECG recordings and over reads of measurements and reporting of ECG tracings by a cardiologist.

In the data presentation that follows, only data from the studies using the methodology for ECG capture described above are provided. In these studies, baseline ECGs were obtained at study enrollment. Subsequent ECGs were obtained at end of treatment, and depending on the length of the study, at intervals during treatment. Thus there are relatively few ECGs for a given subject. It should also be noted that on-treatment ECGs were not timed with respect to timing of dose but rather represent steady state exposure to drug. As quetiapine is known to increase heart rate (see current prescribing information in Appendix E), data for QTc Fridericia (QTcF), the most appropriate correction factor, are shown.

**QT findings**

Mean changes in QTcF for quetiapine (IR and XR pooled) compared with placebo were generally small and not clinically meaningful. In Pool B, placebo-controlled short-term studies, of ≤12 weeks duration), from baseline to end of treatment, least squares mean change for quetiapine (n=8214) versus placebo (n=4026) was 0.46 ms (95% CI: -0.22, +1.14). The change from baseline to maximum value was similar 0.37 ms (95% CI: -0.31, +1.05).

Shifts in QTcF to potentially clinically important values for Pool A (all studies in all indications) are presented in Table 33. There is considerable variability in QT/QTc values in the same patient at different times due to a number of factors unrelated to study treatment (eg, diurnal variation, meals, posture, activity, autonomic factors, heart rate, other treatments). For these reasons, isolated QTc shifts may be relatively nonspecific although patients with both QTcF increased from baseline ≥60 ms and QTcF ≥500 ms do represent a group of potential clinical interest (FDA ICH E14 Guidance 2005).

**Table 33 Shifts in QTcF to potentially clinically important values in Pool A (all studies)**

| Treatment | Patients with ECG finding | Total patients[a] | Exposure[c] | Incidence rate/100 pt years[b] |
|---|---|---|---|---|
| QTcF increase from baseline ≥60 ms | | | | |
| Quetiapine | 50 | 15470 | 4256.4 | 1.174 |
| Placebo | 13 | 5239 | 1057.6 | 1.229 |
| QTcF ≥500 ms from baseline (baseline <500 ms) | | | | |
| Quetiapine | 5 | 15464 | 4259.0 | 0.117 |
| Placebo | 2 | 5237 | 1057.1 | 0.189 |
| QTcF ≥500 ms with a QTcF increase from baseline ≥60 ms | | | | |
| Quetiapine | 2 | 15464 | 4259.1 | 0.047 |
| Placebo | 0 | 5237 | 1057.2 | 0.000 |

[a] Patients must have received at least one dose of study medication, a baseline and at least one post baseline assessment.
[b] Values are 100 times the total number of patients with event/total exposure.
[c] Exposure in patient-years, censored at first assessment with shift.
Pla Placebo. QTcF QT interval corrected for heart rate using Fridericia's formula

For QTcF values with an increase from baseline of ≥60 ms or for an increase in value of ≥500 ms, the number of patients with these ECG findings treated with quetiapine is relatively small, occurring at an incidence rate/100 pt years of 1.174 and 0.117 respectively. The incidence rate with quetiapine was not greater than the incidence rate with placebo (1.229 and 0.189 respectively). For an increase in baseline of ≥60 ms, the majority of patients receiving quetiapine had confounding factors that may have contributed to the shifts in the QTcF interval.

Two patients, among the more than 15,000 patients enrolled in clinical studies since 2001, were found to have a QTcF ≥500 ms (513 and 504 ms respectively) combined with an increase in QTcF from baseline of ≥60 ms (70 and 79 ms respectively) versus no identified cases in the more than 5,000 patients in the placebo group. Both patients were in the MDD program. The ECG findings in both cases were incidental (in one case reported after approximately 69 weeks of treatment with quetiapine XR 150 mg/day and in the second case after 4 weeks of treatment with quetiapine XR 100 mg). The first patient reported an AE of "dizziness upon arising from sleep" but the AE of dizziness was not temporally related to the ECG findings. No SAEs were reported for either patient. Both patients completed the study without sequelae.

No patients treated with the higher doses of quetiapine approved for the treatment of schizophrenia and bipolar disorder had a QTcF ≥500 ms combined with an increase in QTcF from baseline of ≥60 ms. Thus it appears that the 2 cases of an increase in QTcF to ≥500

msec combined with an increase in QTcF from baseline of ≥60 ms are likely to be due to factors other than treatment with quetiapine, given the overall low frequency with which this ECG finding was seen, the lack of an apparent dose effect, and the absence of clinical correlates or sequelae. Moreover, there is no evidence of an increased propensity to more substantial QT/QTcF increases across the dose ranges used in these studies and in these patient populations, based on the similar low incidence in the quetiapine and placebo groups of patients who have either an increase in QTcF from baseline of ≥60 ms or an increase in QTcF to ≥500 ms.

### 4.4.8 Adverse events in clinical study database indicating a potential proarrhythmic effect

Reports describing events that may be suggestive of a significant proarrhythmic effect and/or QT prolongation were identified by searching for terms listed within the standardized MedDRA query (SMQ) for QT prolongation and torsade de pointes, using "Standard MedDRA query (broad) - QT and torsade de pointes terms" (http://meddramsso.com/MSSOWeb/SMQ/index.htm).

Table 34 presents the results of this search, including the events resulting in death already discussed in the previous section, for Pool A, the all studies pool.

**Table 34 Adverse events of interest in Pool A (all studies)**

| Treatment | Patients with event (SAE) | Total patients[a] | Exposure[b] | Incidence rate per 100 patient-years (SAE)[c] |
|---|---|---|---|---|
| **Standard MedDRA query (broad) - QT and torsade de pointes terms** | | | | |
| Quetiapine | 251 (46) | 26454 | 7890.0 | 3.18 (0.58) |
| Placebo | 21 (1) | 6375 | 1196.7 | 1.75 (0.08) |
| Comparator | 20 (5) | 4001 | 787.4 | 2.54 (0.63) |
| **Standard MedDRA query (broad) - QT and torsade de pointes terms, excluding terms "syncope" and "syncope vasovagal"** | | | | |
| Quetiapine | 67 (20) | 26454 | 7890 | 0.8 (0.25) |
| Placebo | 7 (0) | 6375 | 1196.7 | 0.6 (0.00) |
| Comparator | 9 (4) | 4001 | 787.4 | 1.1 (0.51) |

[a] Patients must have received at least 1 dose of study medication.
[b] Exposure in patient-years.
[c] Values are 100 times the total number of patients with event/total patient years of exposure.
Note: Based on the variable adverse-event-outcome in the safety database.MedDRA Medical dictionary for regulatory activities; SAE Serious adverse event.

The following AEs terms (included in the QT and torsade de pointes SMQ) were not identified in the clinical studies database in Pool A (all studies): "cardiac death", "ECG QT

interval abnormal", "ECG U-wave abnormality", "long QT syndrome congenital", "torsade de pointes", or "ventricular fibrillation".

For individual PTs which were reported in this SMQ, for quetiapine the most frequently reported events were "syncope"/"vasovagal syncope" (AEs [SAEs]: 175 [24]/10 [2]), "electrocardiogram QT prolonged" 24 [1], "loss of consciousness" 30 [7]. It is important to note that syncope is a recognized AE associated with the use of quetiapine, independent of any potential proarrhythmic effect. Quetiapine, like other antipsychotics with alpha 1 adrenergic-blocking activity, may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. The effects of quetiapine on heart rate and blood pressure in adults have been well characterized in clinical studies and are described in the current product label.

Because of the potential confounding effect of syncope on the interpretation of these results, this analysis was also performed excluding the events of syncope and vasovagal syncope. When these terms were excluded, there was no significant difference in the relative risk for quetiapine compared with placebo. There were no apparent differences across indications including the MDD and GAD group (a total of 6 events: "electrocardiogram QT prolonged" (4) for quetiapine, loss of consciousness (1 each for quetiapine and placebo). None of these events were reported as SAEs for MDD and GAD.

No patients with reports of syncope had ECGs during the study with a QT interval corrected for heart rate using Fridericia's formula (QTcF, Fridericia 1920) greater than 500 ms. One subject randomized to quetiapine 600 mg and lithium with report of syncope on 04 November 2004 (recorded as mild) had a shift from baseline in QTcF of greater than 60 ms on recorded on 27 December 2004. This patient was also started on quinine after the baseline ECG was conducted and was receiving it during the time that the on treatment ECG was recorded.

Additionally, for the SMQ of convulsions, there were no significant differences between quetiapine and placebo; either in Pool A, the all studies pool, or in Pool B, the placebo-controlled short-term studies pool.

### 4.4.9 Post-marketing reports of adverse events indicating a potential proarrhythmic effect

It has been estimated that about 22 million patients worldwide have been exposed to quetiapine since its launch through the end of February 2008 (see Appendix A4 for details). A review was performed of all quetiapine/quetiapine XR post-marketing reports in the global clinical safety database describing events of QT prolongation, torsade de pointes, and arrhythmias of interest (ventricular tachycardia, ventricular fibrillation, ventricular arrhythmia). A total of 252 reports containing 1 or more of these terms were identified. Of these, 11 reports had a fatal outcome. Fourteen of the 252 reports contained the reported term of torsade de pointes; none of these 14 reports described a fatal outcome.

Overall, these reports contained insufficient information, thereby limiting assessment, and/or described confounding factors that may have contributed to the reported events (eg,

concomitant medical conditions, electrolyte abnormalities, and/or concomitant use of medication known to cause prolongation of QT interval or arrhythmia).

### 4.4.10 Safety data from the Food and Drug Administration's Adverse Event Reporting System

For events possibly related to sudden cardiac death, cardiac arrhythmia and ventricular tachyarrhythmia, the FDA's Adverse Event Reporting System (AERS) database was searched through the third quarter of 2008. Methods were as described in Section 4.2.8.2.

A search was performed using terms possibly associated with sudden cardiac death FDA ICH E14 Guidance 2005, Ray et al 2009), using the same terms as used in the analysis of the clinical study database (combined PTs of sudden death, sudden cardiac death, cardiac death, cardiac arrest, cardio-respiratory arrest) analyzing reports of quetiapine/quetiapine XR as a suspect and concomitant drug. An analysis of these combined events showed quetiapine has a similar EB05 when compared with other typical and atypical antipsychotics, SSRIs, SNRIs, MAO inhibitors, and TCAs.

Additionally, a search was performed using terms related to ventricular tachyarrhythmia (combined PTs of parasystole, rhythm idioventricular, torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachycardia, accelerated idioventricular rhythm, ventricular pre-excitation, cardiac fibrillation, and ventricular tachyarrhythmia). For the search term "electrocardiogram QT prolonged", the EB05 for quetiapine was broadly similar to the atypical and typical antipsychotics as well as TCAs, but higher than the SSRI, SNRIs and MAO inhibitors. However, an analysis of terms classified as "ventricular tachyarrhythmias" showed quetiapine has similar EB05 to other typical and atypical antipsychotics, SSRIs, SNRIs, MAO inhibitors, and TCAs.

### 4.4.11 Conclusions on sudden cardiac death

In a study using a retrospective analysis of a Medicaid database, Ray et al 2009 reported that current users of typical and atypical antipsychotic drugs, including quetiapine, had higher rates of SCD than did nonusers. His study suggested that patients exposed to lower doses of atypical antipsychotic drugs, including quetiapine, had a lower risk of sudden cardiac death compared with users of higher doses.

An evaluation of overall mortality, sudden cardiac death (including a blinded adjudication by an external cardiologist), QT data, and adverse event terms indicating potential proarrhythmic effects from clinical trials and post marketing databases was conducted.

- ***These analyses did not identify a higher risk of sudden cardiac death among patients treated with quetiapine compared to those treated with placebo.***

# 5. RISK MANAGEMENT IN MDD AND GAD

The US package insert (USPI) and Medication Guide are the primary framework through which risks associated with quetiapine XR in MDD and GAD will be communicated to healthcare professionals and patients. In addition, AstraZeneca will conduct post approval safety surveillance and further post approval studies as agreed with FDA.

## 5.1 Product labeling

### 5.1.1 Product label for Health Care Providers (see Appendix E, US Product Information for Seroquel)

The proposed USPI for Seroquel XR in MDD and GAD clearly communicates the risks of interest. The proposed labeling contains clear, high-quality instructions to healthcare providers in the product label regarding the following potential long-term risks:

- ***Tardive Dyskinesia (TD)***
  The SEROQUEL US PI (see Appendix E) includes a warning, similar to that for all antipsychotics, for tardive dyskinesia, which informs how it should be prescribed in a manner that minimizes the occurrence of tardive dyskinesia. Part of the warning includes the statement that "chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that is (1) known to respond to antipsychotics drugs and (2) for whom alternative, equally treatments, but potentially less harmful treatments, are not available or appropriate". It continues, "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 XR, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome."

- ***Hyperglycemia, diabetes, weight gain, and hyperlipidemia***
  In the SEROQUEL US Product Information (see Appendix E), there are warnings for hyperglycemia, diabetes, weight gain, and hyperlipidemia. Part of the warning for hyperglycemia informs "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."

The warnings for weight gain, hyperglycemia and hyperlipidemia display changes observed in clinical studies using quetiapine.

### 5.1.2 Medication guide for patients

The current prescribing information for SEROQUEL XR has an existing medication guide that has been implemented for all antidepressants, informing patients of a potential risk of suicidality.

AstraZeneca has proposed a revision to the Medication Guide in the MDD and GAD submissions. The revised Medication Guide will be distributed consistent with the guidelines set forth by FDA. The revised Medication Guide provides benefit-risk information using patient-friendly language that has been tested for readability. In particular, the revised Medication Guide contains information regarding hyperglycemia, diabetes, hyperlipidemia, weight gain and tardive dyskinesia. This will include, but is not limited to:

- "Tell your doctor about being very thirsty or hungry, feeling weak, or passing lots of urine. These are signs of high blood sugar (hyperglycemia) or diabetes. High blood sugar can be life threatening or even cause death."
- "Tell your doctor about any movements of the face, tongue, or other body parts that you cannot control. These are signs of tardive dyskinesia (TD). Sometimes, TD does not go away."
- Patients are also advised that other important risks include high cholesterol.
- Patients are also advised to tell their doctor, before they start treatment, if they have high cholesterol or triglycerides, heart problems, or if they or their family members have diabetes.
- Patients are also advised that weight gain and increased hunger are common side effects.

Final labeling will be made in accordance with FDA guidance.

## 5.2 Pharmacovigilance

### 5.2.1 Routine pharmacovigilance

Existing routine pharmacovigilance for quetiapine include regular monitoring of the AstraZeneca database of post-approval safety data using targeted medical event terms to focus on identified and potential risks and ongoing product safety and product information reviews. Risks of interest are carefully monitored for change in frequency, severity, or characteristics through routine pharmacovigilance activities that include, but are not limited to, the following:

- Systems and processes that ensure that information about all suspected adverse reactions reported to company personnel are collected and collated in an accessible manner.

- Continuous monitoring of the safety profile of quetiapine/quetiapine XR including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities.

- An internal cross-functional benefit:risk team that meets on a regular basis to monitor the safety profile of quetiapine/quetiapine XR, identify any changes in the benefit:risk profile for quetiapine/quetiapine XR, and initiate any appropriate follow up.

Other pharmacovigilance activities related to safety surveillance of clinical study data and postmarketing data are also established.

### 5.2.2 Post approval studies

AstraZeneca is committed to the post approval evaluation of quetiapine XR treatment and potential long term safety risks of diabetes and tardive dyskinesia in the MDD and GAD populations. We are in the process of eliciting and incorporating input from academic and regulatory experts to evaluate a range of study designs and healthcare databases and identify those with the greatest potential to provide robust, meaningful information. The time frame will be agreed with FDA.

# 6. BENEFIT-TO-RISK PROFILE SUMMARY

## 6.1 Benefit to risk profile

MDD and GAD are highly prevalent and highly disabling psychiatric disorders. Both disorders exert a tremendous toll on the affected individuals, their families, and society as a whole. Despite high prevalence and the availability of a multitude of treatment options, there remain many unmet medical needs, especially with regard to diagnosis, treatment, and outcome. The consequences of not recognizing and treating these disorders can result in increased morbidity, disability, and sometimes death, most often by suicide.

Clinical practice guidelines generally favour SSRIs or SNRIs as first-line pharmacotherapy for both disorders (American Psychiatric Association 2000). The antidepressants, while comparable in their efficacy profile (Mann 2005), are diverse in their side effect profile, often resulting in tolerability issues, which further complicates the medical management of these individuals. In light of this complex symptom presentation, and the specific tolerability issues with each of the currently approved treatments, physicians often change medications to address the specific medical requirements of each individual patient.

For most physicians, the deciding factor in choosing a drug is an understanding of the known pharmacologic profile, the drug's benefit risk profile, and patient's medical history choice. Classes of medications are defined based upon their mechanism of action (eg, SSRIs, SNRIs, TCAs, MAOIs). Different side-effect profiles are associated with these different classes (see Table 1). Some of the side effects associated with antidepressant medications include nausea/vomiting (SSRIs and SNRIs), worsening anxiety/activation (SSRIs, SNRIs), sexual

side effects (SNRIs, SSRIs, TCAs, MAOIs), hypotension (TCAs, MAOIs), sedation (TCAs, mirtazapine), insomnia (SSRIs, SNRIs), weight loss (SSRIs, SNRIs), weight gain (SSRIs, especially paroxetine, TCAs, mirtazapine), cardiotoxicity (TCAs), hypertension (SNRIs, MAOIs), akathisia (SSRIs, SNRIs), and akathisia and tardive dyskinesia (aripiprazole).

Even despite the breadth of treatment options currently available, many MDD and GAD patients fail to achieve an adequate response even after multiple cycles of drug therapy, and new options are required.

Based upon available data, AstraZeneca believes that quetiapine XR is an appropriate option for some patients in the treatment of MDD and GAD. AstraZeneca acknowledges that there are differences in the risk benefit profile of quetiapine XR in comparison to other marketed compounds. However, in light of quetiapine XR's proven efficacy across a wide spectrum of mood symptoms, its established and well characterized safety profile from both clinical studies and post marketing data, and its unique mechanism of action, quetiapine XR is a valuable addition to the existing pharmacological treatment options for both MDD and GAD.

The benefits of quetiapine XR in MDD and GAD, and the risks in both indications, are summarised below.

### 6.1.1 Benefits of quetiapine XR in MDD

Quetiapine XR demonstrated robust efficacy against placebo in the treatment of MDD, at doses of 50 mg, 150 mg, and 300 mg. Superior efficacy was demonstrated in 7 of 8 clinical studies, including studies where quetiapine XR was used in acute treatment as monotherapy and adjunct therapy, and as long-term maintenance therapy. Quetiapine XR has the potential to offer distinct advantages for the treatment of MDD:

- ***An effective antidepressant across a wide spectrum of symptoms***
  Quetiapine XR in doses of 50 mg, 150 mg, and 300 mg was shown to effectively treat MDD in patients with moderate to severe depressive symptoms. In a study with an active comparator, efficacy of each dose was shown to be comparable to that of duloxetine. Efficacy was also shown in elderly patients.

- ***An effective antidepressant with rapid onset of effect***
  Early improvement of depressive symptoms was observed in all studies, for all doses, at the first visit after starting quetiapine XR. In a study with an active comparator, quetiapine XR was significantly superior to duloxetine in reducing depressive symptoms during the first week.

- ***An effective agent as adjunct to existing antidepressant therapy***
  In MDD patients with moderate to severe depressive symptoms, who had had an inadequate response to one or more antidepressants, quetiapine XR at 150 mg and 300 mg was shown to be effective as an adjunctive therapy.

- ***Long-term efficacy***
  As maintenance treatment over a dose range 50 to 300 mg/day, quetiapine XR demonstrated a risk reduction of 66% relative to placebo in preventing recurrence of depressive symptoms.

### 6.1.2 Benefits of quetiapine XR in GAD

Quetiapine XR demonstrated robust efficacy against placebo in the treatment of GAD, at doses of 50 mg, 150 mg, and 300 mg. Superior efficacy was demonstrated in 5 of 5 clinical studies, including studies where quetiapine XR was used in acute treatment as monotherapy and as long-term maintenance therapy. Quetiapine has the potential to offer distinct advantages for the treatment of GAD:

- ***An effective anxiolytic across a wide spectrum of symptoms***
  Quetiapine XR in doses of 50 mg, 150 mg, and 300 mg was shown to effectively treat GAD. In two studies with an active comparator, efficacy of each dose was shown to be comparable to that of escitalopram and paroxetine, respectively. Efficacy was also shown in elderly patients.

- ***An effective anxiolytic with rapid onset of effect***
  Early improvement of anxiety symptoms was observed in all studies, for all doses at the first visit (Day 4 or Week 1) after starting quetiapine XR.

- ***Long-term efficacy***
  As maintenance treatment, quetiapine XR at a dose range of 50 to 300 mg/day demonstrated a risk reduction of 81% relative to placebo in preventing recurrence of anxiety symptoms.

### 6.1.3 Risks of quetiapine XR in MDD and GAD

As with other currently approved agents utilized in the treatment of MDD or GAD, quetiapine XR is not free of potential safety risks. Quetiapine XR has a different safety and tolerability profile from existing agents, and therefore provides another option to clinicians and patients who are trying to find the balance between efficacy and tolerability.

The safety of quetiapine XR in MDD and GAD was examined in the context of a well-known and established safety profile. Quetiapine (quetiapine and quetiapine XR) has been approved for over 11 years and has been prescribed to over 22 million patients worldwide. No new potential risks were identified in the treatment of MDD and GAD beyond those observed with quetiapine in other indications (schizophrenia and bipolar disorder).

#### 6.1.3.1 General side effect profile

Quetiapine XR has a different side effect profile compared with established antidepressants.

- ***Common adverse events are somnolence, sedation, dry mouth, constipation, and headache.*** In the schizophrenia and bipolar patient populations, quetiapine XR's

side effect profile is well characterized and manageable at higher doses (up to 800 mg/day) than are proposed for MDD and GAD (50 to 300 mg/day).

- ***Some of quetiapine XR's side effects are similar to aripiprazole, an atypical antipsychotic approved for adjunctive therapy in MDD*** (eg, potential risks for extrapyramidal symptoms, weight gain, tardive dyskinesia, neuroleptic malignant syndrome, and lipid and glucose changes).

- ***Some of quetiapine XR's side effect are similar to those of certain antidepressants*** (eg, dry mouth, sedation, somnolence, and dizziness are seen with TCAs, mirtazapine, and trazodone; weight gain is seen with TCAs, mirtazapine, and some SSRIs, eg, paroxetine; tardive dyskinesia is seen with aripiprazole, and is included in the labels for amitriptyline, bupropion, buspirone, and venlafaxine XR as post marketing observations; lipid elevations are seen with desvenlafaxine and venlafaxine).

- ***Some side effects of currently marketed antidepressants are not seen or occur rarely with quetiapine XR*** (eg, potential for serotonin syndrome seen with SSRIs and SNRIs; hypertension seen with SNRIs and MAOIs, induction of manic or hypomanic event, seen with many SSRIs and SNRIs)

#### 6.1.3.2 Specific potential long-term risks

**Metabolic parameters**

- ***Within the MDD/GAD program, where lower daily doses are used (50 to 300 mg/day), the mean changes in metabolic variables appeared generally similar to, or smaller than, those seen in studies in indications using higher doses (up to 800 mg/day).***

- ***Within the overall clinical study program and the MDD/GAD studies, there was no evidence that quetiapine XR was associated with adverse events potentially related to atherosclerotic cardiovascular disease.*** In addition, no signal was detected in a review of the AERS database.

- ***Considering all of the available clinical study data, there was no consistent trend for increasing risk of adverse events potentially related to diabetes with quetiapine.*** Within the MDD/GAD studies there was no evidence that quetiapine XR was associated with adverse events potentially related to diabetes. An increased number of adverse events potentially related to diabetes was reported in the long-term randomized withdrawal studies, but not in the placebo-controlled short term studies.

- ***Evaluation of metabolic data from the MDD and GAD populations did not reveal any metabolic findings, or suggest a potential long term metabolic risk inconsistent with those seen in the currently approved indications of schizophrenia and bipolar disorder.***

**Tardive dyskinesia**

- ***While there exists a risk of TD with quetiapine, as indicated in the product labeling, this risk is low, as supported by the frequency of TD AEs associated with quetiapine in clinical studies across all indications (0.2%, 53/26454 patients).*** Results suggest that the risk of TD may be lower in the MDD and GAD populations than in schizophrenia and bipolar patients treated with quetiapine.

**Sudden cardiac death**

- ***The analyses did not identify a higher risk of sudden cardiac death among patients treated with quetiapine compared to those treated with placebo.***

A complete label that informs the reader about benefits and risks will best serve the judgement of the prescribing physicians regarding the suitability of quetiapine XR for the treatment of individual patients.

## 6.2 Weighing the benefits and risks

Quetiapine XR demonstrated robust efficacy against placebo in the treatment of MDD and GAD, two highly debilitating diseases. With many existing treatment options like SSRIs, SNRIs, MAOIs, TCAs and one atypical antipsychotic, patients continue to fail treatment due to lack of response or tolerability issues. Some approved agents for MDD and GAD carry metabolic risks while others carry risks for tardive dyskinesia.

MDD and GAD occur along a continuum from mild symptom presentation, where medications may or may not be needed, to severe symptoms where the suffering, and the potential for poor outcomes, including suicide, are considerable. The general consensus across treatment guidelines is that first-line pharmacotherapy for patients with MDD or GAD should consist of either an SSRI or an SNRI. Ultimately, it is up to the physician to make an appropriate diagnosis, and discuss treatment options and inform the patient of risks associated with the treatment. The benefit to risk assessment is made on an individual basis. In doing so, the physician should discuss the benefit of the proposed treatments, alternative treatments, and the risk of no treatment at all. In weighing these options, the physician should consider the following:

- The presenting symptoms and severity of the patient's illness
- Potential for self-harm
- Prior medication history
- Medical and psychiatric comorbidities
- The patient's willingness to comply with treatment
- Concomitant medication use

- Current functioning of the patient

There is no single medication that is effective for all patients. More importantly, there is no clear path of treatment options for patients to take. Current treatment guidelines recommend that alternative treatments should be considered if the patient has an inadequate response to treatment, or experiences a problematic side effect. Because many patients do not respond to initial treatment, clinicians often switch from one medication to another in order to achieve efficacy as well as tolerability.

Quetiapine XR is a valuable addition to clinicians striving to optimize the treatment of depression in individual patients. Quetiapine XR has in multiple clinical studies been shown to effectively treat MDD as monotherapy and adjunct acute treatment, and for long-term maintenance treatment; and GAD in monotherapy acute treatment and for long-term maintenance treatment. Just as for other approved agents, the use of quetiapine XR in the treatment of MDD and GAD is not without risks. Quetiapine XR represents a needed alternative pharmacologic option and a valuable addition to approved treatment options.

# 7. SUMMARY AND CONCLUSIONS

Quetiapine XR's benefit and risks have been sufficiently well characterised in a comprehensive clinical development program to appropriately label this unique antidepressant and anxiolytic. With appropriate risk management, quetiapine XR offers patients and prescribers a much needed treatment alternative and a valuable addition to treatment options for both MDD and GAD.

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# 9. APPENDICES

# Appendix A General safety data

General adverse event data from the MDD and GAD programs are presented below in tabular format for the following pools: the short-term adjunct MDD studies (Studies 6 and 7), Pool E (randomized withdrawal studies in MDD and GAD, Studies 5 and 12), and the short-term elderly studies (Studies 14 and 15).

## Appendix A1 Short-term adjunct MDD studies

The number and % of patients with various types of AEs are summarized by treatment group for the short-term adjunct therapy MDD studies in Table 35.

**Table 35 AE incidence – adjunct therapy studies (Studies 6 and 7)**

| Type of adverse event | PLA (N=309) n (%) | QTP 150 (N=315) n (%) | QTP 300 (N=312) n (%) |
|---|---|---|---|
| At least one adverse event | 186 (60.2) | 231 (73.3) | 252 (80.8) |
| Serious adverse event | 4 (1.3) | 3 (1.0) | 3 (1.0) |
| Adverse event leading to death | 0 | 0 | 0 |
| Drug-related adverse event | 92 (29.8) | 188 (59.7) | 218 (69.9) |
| Withdrawals due to adverse event | 6 (1.9) | 28 (8.9) | 48 (15.4) |

N Number of patients in treatment group. n Number of patients in the analysis subset. PLA Placebo. QTP Quetiapine XR.
Note: Patients with multiple events in the same category are counted only once in that category.
Note: Percentages are calculated as n/N*100.
Serious: an event that satisfied 1 or more of the following criteria: was fatal, life-threatening, or a congenital abnormality; required or prolonged hospitalization; required medical or surgical intervention to prevent permanent impairment or damage; or resulted in disability or incapacity.

In the adjunct therapy pool (Studies 6 and 7), the incidence of AEs was 60.2% for the placebo group, 73.3% for the 150 mg/day quetiapine XR group, and 80.8% for the 300 mg/day quetiapine XR groups. A similar pattern was seen for the incidence of drug-related AEs and AEs leading to withdrawal. The incidence of SAEs was low and similar in the placebo (1.3%), the 150 mg/day quetiapine XR group (1.0%), and the 300 mg/day quetiapine XR group (1.0%). There were no AEs leading to death in these studies.

The incidence of common AEs (those occurring with an incidence of ≥5% in any treatment group) by preferred term is summarized by treatment for the pooled short-term adjunct therapy MDD studies in Table 36.

**Table 36 Common adverse events (≥5%) by decreasing incidence – adjunct studies (Studies 6 and 7)**

| MedDRA preferred term | PLA (N=309) n (%) | QTP 150 (N=315) n (%) | QTP 300 (N=312) n (%) |
|---|---|---|---|
| Dry mouth | 24 (7.8) | 86 (27.3) | 124 (39.7) |

**Table 36 Common adverse events (≥5%) by decreasing incidence – adjunct studies (Studies 6 and 7)**

| MedDRA preferred term | PLA (N=309) n (%) | QTP 150 (N=315) n (%) | QTP 300 (N=312) n (%) |
|---|---|---|---|
| Somnolence | 11 (3.6) | 71 (22.5) | 81 (26.0) |
| Sedation | 13 (4.2) | 41 (13.0) | 54 (17.3) |
| Dizziness | 20 (6.5) | 36 (11.4) | 36 (11.5) |
| Fatigue | 12 (3.9) | 45 (14.3) | 34 (10.9) |
| Constipation | 11 (3.6) | 18 (5.7) | 33 (10.6) |
| Headache | 36 (11.7) | 36 (11.4) | 24 (7.7) |
| Nausea | 22 (7.1) | 22 (7.0) | 24 (7.7) |
| Weight increased | 1 (0.3) | 10 (3.2) | 16 (5.1) |
| Insomnia | 17 (5.5) | 19 (6.0) | 14 (4.5) |

Patients with multiple events falling under the same preferred term are counted only once in that term.
Note: Common AEs: AEs occurring at an incidence of ≥5% in any treatment group.
PLA Placebo. QTP Quetiapine XR.
MedDRA Medical Dictionary for Regulatory Affairs, version 10.

# Appendix A2 Maintenance (randomized withdrawal) MDD and GAD studies

A summary of AEs in each category for the open-label phases of Studies 5 and 12 is presented in Table 37.

**Table 37 AE incidence – open-label phase (Studies 5 and 12)**

| Category of adverse event | QTP N=3078 n (%) |
|---|---|
| Any adverse event | 2648 (86.0) |
| Serious adverse event | 54 (1.8) |
| Serious adverse event leading to death | 3 (0.1) |
| Serious adverse event not leading to death | 51 (1.7) |
| Drug-related adverse event[a] | 2381 (77.4) |
| Adverse events leading to discontinuation | 605 (19.7) |

[a] As judged by the investigator.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as n/N*100.
N Number of patients in treatment group. n Number of patients. QTP Quetiapine XR.
Serious: an event that satisfied 1 or more of the following criteria: was fatal, life-threatening, or a congenital abnormality; required or prolonged hospitalization; required medical or surgical intervention to prevent permanent impairment or damage; or resulted in disability or incapacity.

During the open-label phase of the studies, the incidence of any AE was 86.0%, and most were considered drug-related (77.4%) by the investigator. The proportion of patients having AEs leading to discontinuation was 19.7%. The incidence of SAEs was low (1.8%). A total of 3 deaths (metastatic neoplasm, myocardial infarction, and death [cause not documented in clinical database]) were reported during the open-label phase; none was considered to be related to study treatment.

A summary of AEs in each category reported for patients in the randomized safety population of Studies 5 and 12 is presented in Table 38.

**Table 38 AE incidence – randomized phase (Studies 5 and 12)**

| | **PLA N=601** | **QTP** N=607 | **Total** N=1208 |
|---|---|---|---|
| **Category of adverse event** | **n (%)** | **n (%)** | **n (%)** |
| Any adverse event | 344 (57.2) | 358 (59.0) | 702 (58.1) |
| Serious adverse event | 11 (1.8) | 11 (1.8) | 22 (1.8) |
| Serious adverse event leading to death | 1 (0.2) | 0 | 1 (0.1) |
| Serious adverse event not leading to death | 10 (1.7) | 11 (1.8) | 21 (1.7) |
| Drug-related adverse event[a] | 157 (26.1) | 181 (29.8) | 338 (28.0) |
| Adverse events leading to discontinuation[b] | 26 (4.3) | 30 (4.9) | 56 (4.6) |

[a] As judged by the investigator.
[b] Interpretation of percentages of patients in the quetiapine XR group who discontinued due to an AE should be considered in light of the longer exposure to study drug in that treatment group compared with the placebo group.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as n/N*100.
N Number of patients in treatment group. n Number of patients. PLA Placebo; QTP Quetiapine XR.
Serious: an event that satisfied 1 or more of the following criteria: was fatal, life-threatening, or a congenital abnormality; required or prolonged hospitalization; required medical or surgical intervention to prevent permanent impairment or damage; or resulted in disability or incapacity.

During the randomized phase of the study, the overall incidence of any AE was comparable between the quetiapine XR and placebo groups (59.0% and 57.2%, respectively). Drug-related AEs were reported slightly more frequently for the quetiapine XR group compared with the placebo group (29.8% and 26.1%, respectively). The incidence of AEs leading to discontinuation was comparable for the quetiapine XR and placebo groups (4.9% and 4.3%, respectively), even though exposure to study drug was considerably higher in the quetiapine XR group. One death (hypertension) was reported for a patient in the placebo group; it was not considered to be related to study treatment. The incidence of non-fatal SAEs was low (≤2%) and comparable for the 2 treatment groups.

The incidence of common AEs (those occurring with an incidence of ≥5% in any treatment group) by preferred term is summarized by treatment for the open-label phase of the maintenance (randomized withdrawal) studies in Table 39 and for randomised phase in Table 40.

**Table 39 Common adverse events (≥5%) by decreasing incidence – open-label phase (Studies 5 and 12)**

| MedDRA preferred term[a] | QTP N= 3078 n (%) |
|---|---|
| Dry Mouth | 859 (27.9) |
| Somnolence | 955 (31.0) |
| Sedation | 673 (21.9) |
| Dizziness | 399 (13.0) |
| Fatigue | 406 (13.2) |
| Constipation | 260 (8.4) |
| Headache | 295 (9.6) |
| Weight Increased | 190 (6.2) |
| Nausea | 195 (6.3) |
| Increased Appetite | 145 (4.7) |
| Nasopharyngitis | 114 (3.7) |
| Irritability | 181 (5.9) |
| Upper respiratory tract infection | 81(2.6) |

[a] Patients with multiple events falling under the same preferred term are counted only once in that term during each phase (open-label or randomized).
Note: Common adverse event is defined as an event occurring at an incidence of ≥5% in any treatment group.
Note: Events reported during randomized phase are sorted by decreasing frequency in the QTP XR group.
MedDRA Medical Dictionary of Regulatory Activities. N Number of patients in treatment group. n Number of patients. QTP Quetiapine XR.

**Table 40 Common adverse events (≥5%) by decreasing incidence – randomized phase (Studies 5 and 12)**

| MedDRA preferred term[a] | PLA N=601 n (%) | QTP N=607 n (%) | Total N=1208 n (%) |
|---|---|---|---|
| Weight increased | 7 (1.2) | 47 (7.7) | 54 (4.5) |
| Headache | 71 (11.8) | 46 (7.6) | 117 (9.7) |
| Nasopharyngitis | 32 (5.3) | 39 (6.4) | 71 (5.9) |
| Dizziness | 23 (3.8) | 32 (5.3) | 55 (4.6) |
| Insomnia | 87 (14.5) | 29 (4.8) | 116 (9.6) |

**Table 40 Common adverse events (≥5%) by decreasing incidence – randomized phase (Studies 5 and 12)**

| | PLA N=601 | QTP N=607 | Total N=1208 |
|---|---|---|---|
| **MedDRA preferred term[a]** | **n (%)** | **n (%)** | **n (%)** |
| Diarrhoea | 33 (5.5) | 28 (4.6) | 61 (5.0) |
| Nausea | 70 (11.6) | 22 (3.6) | 92 (7.6) |

[a] Patients with multiple events falling under the same preferred term are counted only once.
Note: Common adverse event is defined as an event occurring at an incidence of ≥5% in any treatment group.
Note: Events reported during randomized phase are sorted by decreasing frequency in the QTP XR group.
MedDRA Medical Dictionary of Regulatory Activities. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine XR.

# Appendix A3 Elderly studies

**Table 41 AE incidence – elderly studies (Studies 14 and 15)**

| | PLA (N=399) | QTP XR (N=389) | Total (N=788) |
|---|---|---|---|
| **Type of adverse event** | **n (%)** | **n (%)** | **n (%)** |
| At least one adverse event | 219 (54.9) | 279 (71.7) | 498 (63.2) |
| Serious adverse event | 5 (1.3) | 5 (1.3) | 10 (1.3) |
| Adverse event leading to death | 1 (0.3) | 0 | 1 (0.1) |
| Drug-related adverse event | 125 (31.3) | 211 (54.2) | 336 (42.6) |
| Withdrawals due to adverse event | 10 (2.5) | 28 (7.2) | 38 (4.8) |

N Number of patients in treatment group. n Number of patients in the analysis subset. PLA Placebo. QTP Quetiapine XR.
Note: Percentages are calculated as n/N*100.
Note: Patients with multiple events in the same category are counted only once in that category.
Serious: an event that satisfied 1 or more of the following criteria: was fatal, life-threatening, or a congenital abnormality; required or prolonged hospitalization; required medical or surgical intervention to prevent permanent impairment or damage; or resulted in disability or incapacity.

In Studies 14 and 15, the incidence of AEs was 54.9% for the placebo group and 71.7% for the quetiapine XR group. A similar pattern was seen for the incidence of drug-related AEs and AEs leading to withdrawal. The incidence of SAEs was low and similar in the placebo group (1.3%) and the quetiapine XR group (1.3%). There was 1 AE leading to death in these studies.

The incidence of common AEs (those occurring with an incidence of ≥5% in any treatment group) by preferred term is summarized by treatment for the elderly studies in Table 42.

**Table 42 Common adverse events (≥5%) by decreasing incidence – elderly studies (Studies 14 and 15)**

| MedDRA preferred term | PLA (N=399) n (%) | QTP (N=389) n (%) | Total (N=788) n (%) |
|---|---|---|---|
| Somnolence | 33 (8.3) | 113 (29.0) | 146 (18.5) |
| Dry mouth | 34 (8.5) | 71 (18.3) | 105 (13.3) |
| Dizziness | 42 (10.5) | 62 (15.9) | 104 (13.2) |
| Headache | 57 (14.3) | 61 (15.7) | 118 (15.0) |
| Nausea | 17 (4.3) | 29 (7.5) | 46 (5.8) |
| Diarrhoea | 20 (5.0) | 16 (4.1) | 36 (4.6) |

Patients with multiple events falling under the same preferred term are counted only once in that term.
Note: Common AEs: AEs occurring at an incidence of ≥5% in any treatment group during the active treatment and post-treatment periods.
PLA Placebo. QTP Quetiapine XR.
MedDRA Medical Dictionary for Regulatory Affairs.

## Appendix A4 Postmarketing exposure estimates

It has been estimated that about 22.8 million patients worldwide have been exposed to SEROQUEL/SEROQUEL XR since launch through the end of February 2008. This estimate is based upon the following: (1) assumptions as to the number of prescriptions per patient, based upon 2007 United States (US) market research and (2) projections of prescriptions since launch based upon information available in the US (dispensed prescriptions from retail, long-term-care, and mail-order pharmacies) and 12 other countries (Australia, Belgium, Canada, Egypt, Germany, Italy, Japan, Netherlands, Saudi Arabia, Spain, and United Kingdom [written prescriptions from office-based physicians]) in which SEROQUEL/SEROQUEL XR is marketed.

# Appendix B Metabolic data

## Table 43 Number of quetiapine-treated patients with adverse events potentially related to diabetes in Pool A (all studies)

| MedDRA preferred term | Patients with event | Total patients[a] | Incidence rate[b] | Exposure[c] | Incidence density[d] |
|---|---|---|---|---|---|
| Any[e] | 199 (16) | 26454 | 0.75 (0.06) | 7843.0 (7887.8) | 2.5 (0.2) |
| BLOOD GLUCOSE INCREASED | 34 (1) | 26454 | 0.13 (0.00) | 7881.7 (7889.9) | 0.4 (0.0) |
| BLOOD INSULIN ABNORMAL | 0 (0) | 26454 | 0.00 (0.00) | 7890.0 (7890.0) | 0.0 (0.0) |
| BLOOD INSULIN DECREASED | 5 (0) | 26454 | 0.02 (0.00) | 7889.3 (7890.0) | 0.1 (0.0) |
| BLOOD INSULIN INCREASED | 15 (0) | 26454 | 0.06 (0.00) | 7887.3 (7890.0) | 0.2 (0.0) |
| DIABETES MELLITUS | 34 (3) | 26454 | 0.13 (0.01) | 7878.9 (7889.9) | 0.4 (0.0) |
| DIABETES MELLITUS INADEQUATE CONTROL | 4 (2) | 26454 | 0.02 (0.01) | 7887.1 (7888.5) | 0.1 (0.0) |
| DIABETIC COMPLICATION | 1 (1) | 26454 | 0.00 (0.00) | 7890.0 (7890.0) | 0.0 (0.0) |
| DIABETIC KETOACIDOSIS | 3 (3) | 26454 | 0.01 (0.01) | 7889.3 (7889.3) | 0.0 (0.0) |
| GLUCOSE TOLERANCE IMPAIRED | 4 (0) | 26454 | 0.02 (0.00) | 7889.5 (7890.0) | 0.1 (0.0) |
| GLUCOSE TOLERANCE TEST ABNORMAL | 1 (0) | 26454 | 0.00 (0.00) | 7890.0 (7890.0) | 0.0 (0.0) |
| GLUCOSE URINE PRESENT | 3 (0) | 26454 | 0.01 (0.00) | 7888.9 (7890.0) | 0.0 (0.0) |
| GLYCOSURIA | 3 (0) | 26454 | 0.01 (0.00) | 7888.3 (7890.0) | 0.0 (0.0) |
| GLYCOSYLATED HAEMOGLOBIN INCREASED | 15 (0) | 26454 | 0.06 (0.00) | 7888.7 (7890.0) | 0.2 (0.0) |
| HYPERGLYCAEMIA | 32 (6) | 26454 | 0.12 (0.02) | 7882.6 (7889.9) | 0.4 (0.1) |
| HYPERINSULINAEMIA | 9 (0) | 26454 | 0.03 (0.00) | 7887.2 (7890.0) | 0.1 (0.0) |
| IMPAIRED INSULIN SECRETION | 1 (0) | 26454 | 0.00 (0.00) | 7890.0 (7890.0) | 0.0 (0.0) |
| INSULIN RESISTANCE | 5 (0) | 26454 | 0.02 (0.00) | 7889.6 (7890.0) | 0.1 (0.0) |
| POLYURIA | 25 (0) | 26454 | 0.09 (0.00) | 7884.5 (7890.0) | 0.3 (0.0) |
| TYPE 2 DIABETES MELLITUS | 20 (1) | 26454 | 0.08 (0.00) | 7886.3 (7890.0) | 0.3 (0.0) |

[a] Patients must have received at least one dose of study medication.
[b] 100 x total number of patients with event/total number of patients.
[c] Exposure in patient-years, censored at first event.
[d] 100 x total number of patients with event/total patient years of censored exposure.
[e] The number of patients with any of the adverse events. Since a patient can have more than one adverse event, the number does not necessarily equal the sum of the numbers below.
[f] MedDra Lower Level Term Name.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Pgm: Reg-Def\AC 2009\Diabetes Feb 09 FDA\...\AE_all2.SAS. Data version: V17.2. User: kjwm515. 2009-02-27 14:05.

**Table 44 Number of patients with adverse events related to diabetes in Pool B (all placebo-controlled studies)**

| MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | MH incidence rate per 100 pt-yrs[d] | MH relative risk[c] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|
| Any[e] | QTP | 38 (1) | 8853 | 980.6 (981.7) | 4.1 | 0.87 | 0.51 | 1.48 |
| | Pla | 23 (1) | 4359 | 491.3 (492.4) | 4.7 | | | |
| BLOOD GLUCOSE INCREASED | QTP | 8 (0) | 8853 | 981.4 (981.7) | 0.8 | | | |
| | Pla | 6 (0) | 4359 | 492.2 (492.4) | 1.2 | | | |
| BLOOD INSULIN ABNORMAL | QTP | 0 (0) | 8853 | 981.7 (981.7) | 0.0 | | | |
| | Pla | 1 (0) | 4359 | 492.3 (492.4) | 0.2 | | | |
| BLOOD INSULIN DECREASED | QTP | 0 (0) | 8853 | 981.7 (981.7) | 0.0 | | | |
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |
| BLOOD INSULIN INCREASED | QTP | 3 (0) | 8853 | 981.7 (981.7) | 0.3 | | | |
| | Pla | 2 (0) | 4359 | 492.4 (492.4) | 0.5 | | | |
| DIABETES MELLITUS | QTP | 4 (1) | 8853 | 981.7 (981.7) | 0.4 | | | |
| | Pla | 1 (1) | 4359 | 492.4 (492.4) | 0.3 | | | |
| DIABETES MELLITUS INADEQUATE CONTROL | QTP | 0 (0) | 8853 | 981.7 (981.7) | 0.0 | | | |
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |
| DIABETIC COMPLICATION | QTP | 0 (0) | 8853 | 981.7 (981.7) | 0.0 | | | |
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |
| DIABETIC KETOACIDOSIS | QTP | 0 (0) | 8853 | 981.7 (981.7) | 0.0 | | | |
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |
| GLUCOSE TOLERANCE IMPAIRED | QTP | 2 (0) | 8853 | 981.6 (981.7) | 0.2 | | | |
| | Pla | 1 (0) | 4359 | 492.4 (492.4) | 0.2 | | | |
| GLUCOSE TOLERANCE TEST ABNORMAL | QTP | 0 (0) | 8853 | 981.7 (981.7) | 0.0 | | | |
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |
| GLUCOSE URINE PRESENT | QTP | 0 (0) | 8853 | 981.7 (981.7) | 0.0 | | | |

**Table 44 Number of patients with adverse events related to diabetes in Pool B (all placebo-controlled studies)**

| MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | MH incidence rate per 100 pt-yrs[d] | MH relative risk[e] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |
| GLYCOSURIA | QTP | 0 (0) | 8853 | 981.7 (981.7) | 0.0 | | | |
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |
| GLYCOSYLATED HAEMOGLOBIN INCREASED | QTP | 3 (0) | 8853 | 981.7 (981.7) | 0.3 | | | |
| | Pla | 3 (0) | 4359 | 492.4 (492.4) | 0.7 | | | |
| HYPERGLYCAEMIA | QTP | 6 (0) | 8853 | 981.5 (981.7) | 0.7 | | | |
| | Pla | 2 (0) | 4359 | 492.4 (492.4) | 0.3 | | | |
| HYPERINSULINAEMIA | QTP | 1 (0) | 8853 | 981.7 (981.7) | 0.1 | | | |
| | Pla | 1 (0) | 4359 | 492.4 (492.4) | 0.2 | | | |
| IMPAIRED INSULIN SECRETION | QTP | 1 (0) | 8853 | 981.7 (981.7) | 0.1 | | | |
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |
| INSULIN RESISTANCE | QTP | 1 (0) | 8853 | 981.7 (981.7) | 0.1 | | | |
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |
| POLYURIA | QTP | 8 (0) | 8853 | 981.3 (981.7) | 0.8 | | | |
| | Pla | 7 (0) | 4359 | 491.7 (492.4) | 1.4 | | | |
| TYPE 2 DIABETES MELLITUS | QTP | 2 (0) | 8853 | 981.7 (981.7) | 0.3 | | | |
| | Pla | 0 (0) | 4359 | 492.4 (492.4) | 0.0 | | | |

[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years, censored at first event.
[c] The number of patients with any of the adverse events. Since a patient can have more than one adverse event, the number does not necessarily equal the sum of the numbers below.
[d] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[e] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
[f] MedDra Lower Level Term Name.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Study D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.Only the acute phase is included for study D1447C00001 and D1447C00134.
Pgm: Reg-Def\AC 2009\Diabetes Feb 09 FDA\...\AE_pla_ctrl.SAS. Data version: V17.2. User: kjwm515. 2009-02-27 14:18.

**Table 45 Number of patients with adverse events related to diabetes in Pool C (All long-term randomized withdrawal studies)**

| MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | MH incidence rate per 100 pt-yrs[d] | MH relative risk[e] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|
| Any[c] | QTP | 31 (2) | 2043 | 1017.5 (1025.9) | 3.1 | 1.98 | 1.00 | 3.95 |
| | Pla | 11 (2) | 2016 | 702.4 (704.2) | 1.5 | | | |
| BLOOD GLUCOSE INCREASED | QTP | 3 (0) | 2043 | 1024.5 (1026.0) | 0.3 | | | |
| | Pla | 1 (0) | 2016 | 704.2 (704.3) | 0.1 | | | |
| BLOOD INSULIN ABNORMAL | QTP | 0 (0) | 2043 | 1026.0 (1026.0) | 0.0 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| BLOOD INSULIN DECREASED | QTP | 1 (0) | 2043 | 1025.6 (1026.0) | 0.1 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| BLOOD INSULIN INCREASED | QTP | 2 (0) | 2043 | 1025.9 (1026.0) | 0.2 | | | |
| | Pla | 2 (0) | 2016 | 703.4 (704.3) | 0.3 | | | |
| DIABETES MELLITUS | QTP | 4 (0) | 2043 | 1023.8 (1026.0) | 0.4 | | | |
| | Pla | 1 (0) | 2016 | 704.3 (704.3) | 0.1 | | | |
| DIABETES MELLITUS INADEQUATE CONTROL | QTP | 0 (0) | 2043 | 1026.0 (1026.0) | 0.0 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| DIABETIC COMPLICATION | QTP | 0 (0) | 2043 | 1026.0 (1026.0) | 0.0 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| DIABETIC KETOACIDOSIS | QTP | 1 (1) | 2043 | 1025.9 (1025.9) | 0.1 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| GLUCOSE TOLERANCE IMPAIRED | QTP | 0 (0) | 2043 | 1026.0 (1026.0) | 0.0 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| GLUCOSE TOLERANCE TEST ABNORMAL | QTP | 0 (0) | 2043 | 1026.0 (1026.0) | 0.0 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |

## Table 45 Number of patients with adverse events related to diabetes in Pool C (All long-term randomized withdrawal studies)

| MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | MH incidence rate per 100 pt-yrs[d] | MH relative risk[e] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|
| GLUCOSE URINE PRESENT | QTP | 0 (0) | 2043 | 1026.0 (1026.0) | 0.0 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| GLYCOSURIA | QTP | 0 (0) | 2043 | 1026.0 (1026.0) | 0.0 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| GLYCOSYLATED HAEMOGLOBIN INCREASED | QTP | 5 (0) | 2043 | 1025.3 (1026.0) | 0.5 | | | |
| | Pla | 3 (1) | 2016 | 703.7 (704.2) | 0.4 | | | |
| HYPERGLYCAEMIA | QTP | 4 (1) | 2043 | 1024.7 (1025.9) | 0.4 | | | |
| | Pla | 2 (1) | 2016 | 704.3 (704.3) | 0.3 | | | |
| HYPERINSULINAEMIA | QTP | 4 (0) | 2043 | 1024.0 (1026.0) | 0.4 | | | |
| | Pla | 1 (0) | 2016 | 704.3 (704.3) | 0.1 | | | |
| IMPAIRED INSULIN SECRETION | QTP | 0 (0) | 2043 | 1026.0 (1026.0) | 0.0 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| INSULIN RESISTANCE | QTP | 3 (0) | 2043 | 1025.6 (1026.0) | 0.3 | | | |
| | Pla | 0 (0) | 2016 | 704.3 (704.3) | 0.0 | | | |
| POLYURIA | QTP | 1 (0) | 2043 | 1025.8 (1026.0) | 0.1 | | | |
| | Pla | 1 (0) | 2016 | 704.0 (704.3) | 0.1 | | | |
| TYPE 2 DIABETES MELLITUS | QTP | 6 (0) | 2043 | 1025.5 (1026.0) | 0.6 | | | |
| | Pla | 1 (0) | 2016 | 704.3 (704.3) | 0.1 | | | |

[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years, censored at first event.
[c] The number of patients with any of the adverse events. Since a patient can have more than one adverse event, the number does not necessarily equal the sum of the numbers below.
[d] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[e] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
[f] MedDra Lower Level Term Name.
Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events. Only patients with quetiapine treament in the acute phase are included from the continuation phase for study D1447C00001 and D1447C00134. Pgm: Reg-Def\AC 2009\Diabetes Feb 09 FDA\...\AE_pla_ctrl_rp.SAS. Data version: V17.2. User: kjwm515. 2009-02-27 13:59.

**Table 46 Incidence and relative risk of adverse events potentially related to atherosclerotic cardiovascular disease: All cause death, excluding completed suicide and homicide, plus patients with events included in SMQ - Narrow MI or SMQ - Broad CVA, excluding dysarthria in Pool A (all studies)**

| Sub-topic | MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | Incidence rate[c] |
|---|---|---|---|---|---|---|
| Narrow MI related SMQ | Any | QTP | 16(11) | 26454 | 7889.97 | 0.2 |
| | ACUTE CORONARY SYNDROME | QTP | 1(1) | 26454 | 7889.97 | 0.0 |
| | ACUTE MYOCARDIAL INFARCTION | QTP | 3(3) | 26454 | 7889.97 | 0.0 |
| | MYOCARDIAL INFARCTION | QTP | 12(7) | 26454 | 7889.97 | 0.2 |
| All CVA related SMQ excluding term "dysarthria" | Any | QTP | 51(24) | 26454 | 7889.97 | 0.6 |
| | APHASIA | QTP | 7(0) | 26454 | 7889.97 | 0.1 |
| | BRAIN STEM INFARCTION | QTP | 1(1) | 26454 | 7889.97 | 0.0 |
| | CEREBRAL CIRCULATORY FAILURE | QTP | 1(0) | 26454 | 7889.97 | 0.0 |
| | CEREBRAL HAEMATOMA | QTP | 0(0) | 26454 | 7889.97 | 0.0 |
| | CEREBRAL HAEMORRHAGE | QTP | 1(1) | 26454 | 7889.97 | 0.0 |
| | CEREBRAL INFARCTION | QTP | 1(1) | 26454 | 7889.97 | 0.0 |
| | CEREBROVASCULAR ACCIDENT | QTP | 16(14) | 26454 | 7889.97 | 0.2 |
| | CEREBROVASCULAR DISORDER | QTP | 1(0) | 26454 | 7889.97 | 0.0 |
| | HAEMORRHAGIC STROKE | QTP | 1(1) | 26454 | 7889.97 | 0.0 |
| | HEMIPARESIS | QTP | 10(4) | 26454 | 7889.97 | 0.1 |
| | HEMIPLEGIA | QTP | 2(1) | 26454 | 7889.97 | 0.0 |
| | PARALYSIS | QTP | 0(0) | 26454 | 7889.97 | 0.0 |
| | QUADRIPARESIS | QTP | 0(0) | 26454 | 7889.97 | 0.0 |
| | SUBDURAL HAEMORRHAGE | QTP | 1(1) | 26454 | 7889.97 | 0.0 |
| | TRANSIENT ISCHAEMIC ATTACK | QTP | 13(4) | 26454 | 7889.97 | 0.2 |

## Table 46 Incidence and relative risk of adverse events potentially related to atherosclerotic cardiovascular disease: All cause death, excluding completed suicide and homicide, plus patients with events included in SMQ - Narrow MI or SMQ - Broad CVA, excluding dysarthria in Pool A (all studies)

| Sub-topic | MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | Incidence rate[c] |
|---|---|---|---|---|---|---|
| | VERTEBROBASILAR INSUFFICIENCY | QTP | 1(0) | 26454 | 7889.97 | 0.0 |

[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years.
[c] 100 x total number of patients with event/total patient years of exposure.
Note: Based on the variable adverse-event-outcome in the safety database.
Pgm: Reg-Def\Cardiac Feb 09 SERM\...\M_MORT_CV_SUB_data.SAS. Data version: 17.2. User: kjlg762. 2009-02-27 18:20.

## Table 47 Incidence and relative risk of adverse events potentially related to atherosclerotic cardiovascular disease: All cause death, excluding completed suicide and homicide, plus patients with events included in SMQ - Narrow MI or SMQ - Broad CVA, excluding dysarthria in Pool B (all placebo controlled studies)

| Sub-topic | MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | IMH incidence rate per 100pt-yrsd[c] | MH relative risk[d] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|---|
| Narrow MI related SMQ | Any | QTP | 6(3) | 8853 | 981.74 | 0.63 | 0.44 | 0.14 | 1.36 |
| | | PLA | 7(5) | 4359 | 492.41 | 1.43 | | | |
| | ACUTE CORONARY SYNDROME | QTP | 1(1) | 8853 | 981.74 | 0.09 | | | |
| | | PLA | 0(0) | 4359 | 492.41 | 0.00 | | | |
| | ACUTE MYOCARDIAL INFARCTION | QTP | 1(1) | 8853 | 981.74 | 0.12 | | | |
| | | PLA | 0(0) | 4359 | 492.41 | 0.00 | | | |
| | MYOCARDIAL INFARCTION | QTP | 4(1) | 8853 | 981.74 | 0.43 | | | |

**Table 47 Incidence and relative risk of adverse events potentially related to atherosclerotic cardiovascular disease: All cause death, excluding completed suicide and homicide, plus patients with events included in SMQ - Narrow MI or SMQ - Broad CVA, excluding dysarthria in Pool B (all placebo controlled studies)**

| Sub-topic | MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | IMH incidence rate per 100pt-yrsd[c] | MH relative risk[d] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|---|
| | | PLA | 7(5) | 4359 | 492.41 | 1.43 | | | |
| All CVA related SMQ excluding term "dysarthria" | Any | QTP | 6(1) | 8853 | 981.74 | 0.64 | 0.33 | 0.11 | 0.94 |
| | | PLA | 10(4) | 4359 | 492.41 | 1.95 | | | |
| | APHASIA | QTP | 2(0) | 8853 | 981.74 | 0.20 | | | |
| | | PLA | 1(0) | 4359 | 492.41 | 0.21 | | | |
| | BRAIN STEM INFARCTION | QTP | 1(1) | 8853 | 981.74 | 0.09 | | | |
| | | PLA | 0(0) | 4359 | 492.41 | 0.00 | | | |
| | CEREBRAL CIRCULATORY FAILURE | QTP | 1(0) | 8853 | 981.74 | 0.06 | | | |
| | | PLA | 0(0) | 4359 | 492.41 | 0.00 | | | |
| | CEREBRAL HAEMATOMA | QTP | 0(0) | 8853 | 981.74 | 0.00 | | | |
| | | PLA | 0(0) | 4359 | 492.41 | 0.00 | | | |
| | CEREBRAL INFARCTION | QTP | 1(1) | 8853 | 981.74 | 0.09 | | | |
| | | PLA | 1(1) | 4359 | 492.41 | 0.17 | | | |
| | CEREBROVASCULAR ACCIDENT | QTP | 1(1) | 8853 | 981.74 | 0.09 | | | |
| | | PLA | 2(0) | 4359 | 492.41 | 0.33 | | | |
| | CEREBROVASCULAR DISORDER | QTP | 1(0) | 8853 | 981.74 | 0.13 | | | |
| | | PLA | 0(0) | 4359 | 492.41 | 0.00 | | | |
| | HEMIPARESIS | QTP | 0(0) | 8853 | 981.74 | 0.00 | | | |
| | | PLA | 4(2) | 4359 | 492.41 | 0.80 | | | |
| | PARALYSIS | QTP | 0(0) | 8853 | 981.74 | 0.00 | | | |

**Table 47 Incidence and relative risk of adverse events potentially related to atherosclerotic cardiovascular disease: All cause death, excluding completed suicide and homicide, plus patients with events included in SMQ - Narrow MI or SMQ - Broad CVA, excluding dysarthria in Pool B (all placebo controlled studies)**

| Sub-topic | MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | IMH incidence rate per 100pt-yrsd[c] | MH relative risk[d] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|---|
| | | PLA | 1(0) | 4359 | 492.41 | 0.16 | | | |
| | TRANSIENT ISCHAEMIC ATTACK | QTP | 1(0) | 8853 | 981.74 | 0.16 | | | |
| | | PLA | 3(1) | 4359 | 492.41 | 0.61 | | | |

[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years.
[c] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[d] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Based on the variable adverse-event-outcome in the safety database.
Note: Study D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.Only the acute phase is included for study D1447C00001 and D1447C00134.
Pgm: Reg-Def\Cardiac Feb 09 SERM\...\M_MORT_CV_SUB_data.SAS. Data version: 17.2. User: kjlg762. 2009-02-27 18:24.

**Table 48 Incidence and relative risk of adverse events potentially related to atherosclerotic cardiovascular disease: All cause death, excluding completed suicide and homicide, plus patients with events included in SMQ - Narrow MI or SMQ - Broad CVA, excluding dysarthria in Pool C (all long-term randomized withdrawal studies)**

| Sub-topic | MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | MH incidence rate per 100pt-yrsd[c] | MH relative risk[d] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|---|
| Narrow MI related SMQ | Any | QTP | 0(0) | 2043 | 1025.95 | 0.00 | 0.00 | NA | NA |
| | | PLA | 1(1) | 2016 | 704.27 | 0.14 | | | |
| | MYOCARDIAL INFARCTION | QTP | 0(0) | 2043 | 1025.95 | 0.00 | | | |

**Table 48 Incidence and relative risk of adverse events potentially related to atherosclerotic cardiovascular disease: All cause death, excluding completed suicide and homicide, plus patients with events included in SMQ - Narrow MI or SMQ - Broad CVA, excluding dysarthria in Pool C (all long-term randomized withdrawal studies)**

| Sub-topic | MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | MH incidence rate per 100pt-yrsd[c] | MH relative risk[d] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|---|
| | | PLA | 1(1) | 2016 | 704.27 | 0.14 | | | |
| All CVA related SMQ excluding term "dysarthria" | Any | QTP | 1(1) | 2043 | 1025.95 | 0.10 | 0.66 | 0.04 | 10.68 |
| | | PLA | 1(0) | 2016 | 704.27 | 0.15 | | | |
| | HAEMORRHAGIC STROKE | QTP | 1(1) | 2043 | 1025.95 | 0.10 | | | |
| | | PLA | 0(0) | 2016 | 704.27 | 0.00 | | | |
| | QUADRIPARESIS | QTP | 0(0) | 2043 | 1025.95 | 0.00 | | | |
| | | PLA | 1(0) | 2016 | 704.27 | 0.15 | | | |

[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years.
[c] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[d] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Based on the variable adverse-event-outcome in the safety database.
Note: Only patients with quetiapine treament in the acute phase are included from the continuation phase for study D1447C00001 and D1447C00134.
Pgm: Reg-Def\Cardiac Feb 09 SERM\...\M_MORT_CV_SUB_data.SAS. Data version: 17.2. User: kjlg762. 2009-02-27 18:27.

**Table 49 Incidence and relative risk of adverse events potentially related to atherosclerotic cardiovascular disease: All cause death, excluding completed suicide and homicide, plus patients with events included in SMQ - Narrow MI or SMQ - Broad CVA, excluding dysarthria in Pool E (GAD and MDD, all long-term randomized withdrawal studies)**

| Sub-topic | MedDRA preferred term | Treatment | Patients with event | Total patients[a] | Exposure[b] | MH incidence rate per 100pt-yrsd[c] | MH relative risk[d] QTP vs Pla | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|---|---|
| Narrow MI related SMQ | Any | QTP | 0(0) | 607 | 242.02 | 0.00 | NA | NA | NA |
| | | PLA | 0(0) | 601 | 173.74 | | | | |
| All CVA related SMQ excluding term "dysarthria | Any | QTP | 0(0) | 607 | 242.02 | 0.00 | NA | NA | NA |
| | | PLA | 0(0) | 601 | 173.74 | | | | |

[a] Patients must have received at least one dose of study medication.
[b] Exposure in patient-years.
[c] Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
[d] Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Based on the variable adverse-event-outcome in the safety database.
Note: Only patients with quetiapine treament in the acute phase are included from the continuation phase for study D1447C00001 and D1447C00134.
Pgm: Reg-Def\Cardiac Feb 09 SERM\...\M_MORT_CV_SUB_data.SAS. Data version: 17.2. User: kjlg762. 2009-02-27 18:28.

# Appendix C Tardive dyskinesia data

## Appendix C1 Schooler-Kane data

The Schooler-Kane criteria require at least 3 months consecutive exposure to treatment (≥1 month in patients ≥60 years). Thus the analysis was conducted on the two long-term studies in MDD and GAD (Studies 5 and 12), and the two studies in elderly in MDD and GAD (Studies 14 and 15). Patients who met Schooler-Kane criteria at baseline (before 1st treatment dose) were excluded. Patients who met Schooler-Kane criteria any time after baseline or within a 90-day interval after cessation of quetiapine therapy were included in the assessment.

Incidence of TD per Schooler-Kane criteria is presented in Table 50 by study.

**Table 50 Incidence of TD per Schooler-Kane criteria**

| Study[a] | Patients with TD per Schooler Kane criteria by indication | | | | | | |
|---|---|---|---|---|---|---|---|
| | N[b] | n[c] | (%) | Sex (M/F) | Age (y) | Race | TD or EPS related AE |
| Study 5 and 12 (long-term studies) | 2858 | 6 | (0.21) | 2 M, 4 F | M: 61 to 65<br>F: 36 to 62 | 6 W | No |
| Study 14 and 15 (elderly studies) | 384 | 1 | (0.26) | 1 F | F: 71 | 1 W | No |

[a] Presented by study because AIMS data reside in different databases for these studies.
[b] Patients treated with quetiapine who had at least 1 postbaseline AIMS assessment.
[c] Patients who met Schooler-Kane criteria at baseline were excluded. Patients who met criteria any time after baseline or within a 90-day interval after cessation of quetiapine therapy were included. Patients <60 years old without approximately 90 days of quetiapine exposure or ≥60 years without approximately 30 days of quetiapine exposure were not counted. These working criteria were developed in consultation with Dr Kane.

AE Adverse event. BPD Bipolar depression/disorder. EPS Extrapyramidal symptoms.
GAD Generalized anxiety disorder. MDD Major depressive disorder.
TD Tardive dyskinesia. W White.

# Appendix D Sudden cardiac death data

# Appendix D1 Reports of sudden death among patients enrolled in clinical studies

**Table 51 Reports of sudden death among quetiapine patients enrolled in clinical studies, excluding patients enrolled in studies with patients with dementia[a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy)[b] | Preferred terms in database relevant to outcome of death | Clinical Information | Comments |
|---|---|---|---|---|---|
| Quetiapine | | | | | |
| 1997AP31291 | 47/M | Schizophrenia/ 600/34 months | Cardiac arrest | History included schizophrenia, alcohol abuse, elevated liver enzymes, and left bundle branch block on ECG. He had been treated with erythromycin which was reportedly discontinued approximately 6 weeks prior to death. He complained of feeling dizzy, slumped in a chair, and could not be resuscitated. | Adjudicated by external reviewer as a case of sudden death. |
| 1997AP36529 | 60/M | Schizophrenia/ 300 /15 days | Cardiac arrest | History included schizophrenia, angina, and psychosis. Family history of cardiac disease. Medications included trazodone, haldoperidol, temazepam, and acetaminophen. Family history of cardiac disease. Reported to suffer cardiac arrest at the boarding home. CPR was not initiated. | Adjudicated by external reviewer as a case of sudden death. |
| 2001SE05879[c] | 68/F | Bipolar disorder/ 800 /31 days | Cardio-respiratory arrest | History included mania, diabetes, and hypertension treated with carvedilol, lithium, metformin, ramipril, and indapamide. She developed episodic fever and treatment for presumptive malaria was initiated. That night, she became dizzy and found to have a feeble pulse with shallow breathing and a BP of 90/60. Transferred to the ICU where CPR was performed for 30 minutes; no arrhythmia was reported. She | Adjudicated by external reviewer NOT to be a case of sudden death. Reviewer comment: Acute hypotension with multiorgan failure. Investigator reported cardio-respiratory arrest as related to |

**Table 51 Reports of sudden death among quetiapine patients enrolled in clinical studies, excluding patients enrolled in studies with patients with dementia[a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy)[b] | Preferred terms in database relevant to outcome of death | Clinical Information | Comments |
|---|---|---|---|---|---|
| | | | | was successfully resuscitated but required inotropic support to treat a BP of 60 mmHg systolic. She developed renal failure and died 2 days later. | therapy with quetiapine[c]. |
| 1994AP02257[c] | 58/M | Schizophrenia/ 500 / 11 days | Cardio-respiratory arrest | History included schizophrenia as well as hypertension treated with nifedipine and, later, isosorbide dinitrate. A brother had died of a presumed MI. The subject had a history of chest pain for 1 month that was felt to be non cardiac in nature; ECGs showed no evidence of ischemia. Twelve hours prior to death, he developed chest pain, paleness, sweating and hypotension; an ECG was reported to show ischemia. He was reported to experience cardiogenic shock and cardiopulmonary arrest. | Adjudicated by external reviewer NOT to be a case of sudden death. Reviewer comment: Cardiac death but not sudden[c]. |
| 2006UW13843 | 50/F | Bipolar/ 200 /16 days | Cardio-respiratory arrest | History of bipolar disorder and hypothyroidism. Medications included levothyroxine, sulfadiazine and allantoin, lithium, lamotrigine, clonazepam, and naltrexone She died alone at home. | Adjudicated by external reviewer as a case of sudden death. |
| 1997AP34425 | 38/M | Schizophrenia/ 200 /7 months | Sudden Death | History of tobacco use, cardiomegaly, atrioventricular block. Medications included haloperidol, biperiden, flunitrazepam. Failed to attend hospital | Adjudicated by external reviewer as a case of sudden death. |

**Table 51 Reports of sudden death among quetiapine patients enrolled in clinical studies, excluding patients enrolled in studies with patients with dementia[a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy)[b] | Preferred terms in database relevant to outcome of death | Clinical Information | Comments |
|---|---|---|---|---|---|
| | | | | visit and later found dead at home. He had been dead for approximately 10 days. A post-mortem could not be performed due to decay but suicide and homicide were ruled out by the police. | |
| 1998AP44630 | 38/M | Bipolar/600/91 days | Sepsis | History of headache and insomnia. Medications included temazepam, butalbital, acetaminophen, and caffeine. Suffered upset stomach and vomiting. Refused hospitalization and was found dead in bed after 2 days of symptoms. Autopsy showed post-mortem changes in blood vessels suggesting sepsis, bronchopneumonia, aspiration. Inconclusive toxicology. Cause of death determined as probable sepsis. | Adjudicated by external reviewer as a case of sudden death. Reviewer comment: Possible aspiration/sepsis but unclear if caused sudden death. |
| 2005SE06618 | 37/M | Bipolar/800/10 weeks | Cardio-myopathy | History of akathisias, asthmatic bronchitis, sinusitis, and torsion of the testes. No known history of cardiovascular disease. Medications included biperiden. Died at home unwitnessed but had been seen in "good condition" 3 hours previously. Autopsy showed cardiomyopathy. | Adjudicated by external reviewer as a case of sudden death. |
| 2006SE04882 | 50/F | MDD/300/14 days | MI | History of cardiosclerosis, hypertonia, and chronic bronchitis. Medications included valoserdinum for insomnia. Found dead in bed with cause of death reported as MI. No | Adjudicated by external reviewer as a case of sudden death. Reviewer comment: |

**Table 51 Reports of sudden death among quetiapine patients enrolled in clinical studies, excluding patients enrolled in studies with patients with dementia[a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy)[b] | Preferred terms in database relevant to outcome of death | Clinical Information | Comments |
|---|---|---|---|---|---|
| | | | | autopsy. | "MI" without autopsy. |
| 2006UW17146 | 55/F | MDD/300/21 days (last dose 13 days prior to death) | Death | History of cholecystectomy with sepsis. Completed study at which time a prescription for fluoxetine was called into the pharmacy. Not known if the prescription was filled. Patient died in her sleep 2 weeks later. No autopsy was performed but coroner's report stated "probable MI". | Adjudicated by external reviewer as a case of sudden death. |
| 2007UW07296 | 40/M | Bipolar/300/292 days (last dose 2 days prior to death) | Death due to hypertensive cardiovascular disease | History of dizziness, seasonal allergies, conjunctivitis, upper respiratory infection, conjunctivitis. Medications included paracetamol, bismuth subsalicylate, cetirizine, ketoralac, amoxicillin, naproxen. Wife found him foaming at the mouth after going out with friends. CPR was unsuccessful. Autopsy findings consistent with hypertensive heart disease. Toxicology showed only a small amount of ethanol. | Adjudicated by external reviewer as a case of sudden death. |
| 2007UW19364 | 53/M | GAD/300/65 days (last dose approximately 2 months prior to death) | Death cause unknown | History of hyperinsulinemia, gout, acute liver failure due to acetaminophen/ alcohol abuse, hemorrhoids, anemia, thrombocytopenia, seasonal allergies, lymphopenia. Medications included lactulose, cimetidine, cyclobenzaprine, potassium, benzatropine. Found dead in his | Adjudicated by external reviewer as a case of sudden death. |

**Table 51 Reports of sudden death among quetiapine patients enrolled in clinical studies, excluding patients enrolled in studies with patients with dementia[a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy)[b] | Preferred terms in database relevant to outcome of death | Clinical Information | Comments |
|---|---|---|---|---|---|
| | | | | home but likely died prior to that date. | |
| 1998AP45316 | 43/M | Schizophrenia/ 800/1544 days | Cardiac Death | History of atherosclerotic heart disease, alcohol abuse, obesity. Collapsed after drinking 10 beers. Autopsy showed atherosclerosis and hypertensive heart disease. Blood alcohol levels were not sufficiently elevated to contribute to death. | Adjudicated by external reviewer as a case of sudden death. |
| 1998AP50790 | 61/M | Schizophrenia/ 600/54 weeks (last dose 46 weeks prior to death) | Cardiac Arrest | History of tuberculosis but no known cardiac disease at study entry. Diagnosed with heart failure after 8 weeks of treatment with quetiapine. Quetiapine was discontinued and the patient responded to treatment with furosemide, lisinopril, digoxin. Found dead at home 46 weeks after quetiapine discontinued. | Adjudicated by external reviewer as a case of sudden death. |
| 2004SE00487 | 68/M | Psychosis/75/2 months (last dose 4 days prior to cardiac arrest) | Cardiac arrest (non fatal) but subsequent septic shock | History of diabetes, ischemic heart disease, Parkinson's disease, hypertension, hyperuricemia, hypercholesterolemia. Treated with metoprolol, famotidine, cilazapril, allopurinol, hydrochlorothiazide, doxazosin, levodopa, amlodipine, enoxaparin, and aspirin. Suffered cardiac arrest with anoxic brain damage 4 days after last dose of quetiapine. Died of sepsis 2 months later. | Adjudicated by external reviewer as a case of sudden death. |
| 1998AP44951 | 79/M | Pyschosis/300/26 | Cardiac Failure | History included schizophrenia, psychosis, | Adjudicated by |

**Table 51 Reports of sudden death among quetiapine patients enrolled in clinical studies, excluding patients enrolled in studies with patients with dementia[a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy)[b] | Preferred terms in database relevant to outcome of death | Clinical Information | Comments |
|---|---|---|---|---|---|
| | | months | | hypertension. Medications included lorazepam, colace, aspirin. Found apneic and pulseless in bed. Cause of death reported as cardiac failure. | external reviewer as a case of sudden death. |

[a] As discussed in Section 4.4.6.1, the clinical and safety databases were searched for terms describing events mapping to the preferred terms of "sudden death", "sudden cardiac death", "cardiac death", "cardiac arrest", and "cardio-respiratory arrest". Cases in this table that map to other preferred terms were identified by external expert review as described in Section 4.4.6.2.

[b] Patient being treated with quetiapine at time of event unless otherwise indicated in parentheses.

[c] Although adjudicated by external reviewer NOT to be a case of sudden death, the narrative is included for completeness, as the investigator commented on a cardiac-related issue.

Abbreviations: Blood Pressure (BP); Cardiopulmonary Resuscitation (CPR); Electrocardiogram (ECG); Intensive Care Unit (ICU); Myocardial Infarction (MI)

**Table 52 Reports of sudden death among quetiapine patients enrolled in clinical studies in Alzheimer's disease [a]**

| Patient identification number | Age/ sex | Indication/Daily dose (mg)/Time to event [b] | Preferred terms in database relevant to outcome of death | Clinical information | Comments [c] |
|---|---|---|---|---|---|
| Quetiapine | | | | | |
| 1999UW00318 | 89/F | Alzheimer's disease/25/22 days | Cardiac arrest | History included hypertension, PVD, glaucoma, chronic renal failure, bifascicular block. Developed astudy fibrillation and required intubation due to respiratory failure. After extubation, retained $CO_2$ and later suffered a bradycardic arrest resulting in multiorgan failure and death. | Adjudicated by external reviewer as a case of sudden death. Reviewer comment: This was a bradycardiac arrest |
| 1999UW00752[c] | 82/M | Alzheimer's disease/75/115 days | Cardiac arrest | History of falls, ankle edema, decubitus ulcer. Medication included dyazide. Patient broke hip and, after surgery, developed cardiogenic shock with arrhythmias after a probable myocardial infarction. He later suffered a cardiac arrest with anoxic encephalopathy. He was removed from the ventilator and died. | Adjudicated by external reviewer NOT to be a case of sudden death. Reviewer comment: Probable MI after hip surgery [c]. |
| 2003UW13554 | 95/F | Alzheimer's disease/200/44 days | Cardiac arrest | History included CHF, hypertension, hypothyroidism, esophagitis, osteoporosis, arthritis. Medications included valdecoxib, olopatadine, labetalol, zolpidem, lisinopril, raloxifene, isosorbide mononitrate, clonidine, azelastine, lansoprazole, levothyroxine. Found unresponsive, without vital signs. | Adjudicated by external reviewer as a case of sudden death. |
| 1999UW03620 | 82/M | Alzheimer's disease/125 82 days (last dose 23 days prior to death) | Cardio-respiratory arrest | Medical history included cataract, glaucoma, small strokes, MI, heart murmur, gastric resection, bladder cancer. Medications included haloperidol (also reported as suspect), levobunolol. Witnessed cardiac arrest 22 days after the study was completed. | Adjudicated by external reviewer as a case of sudden death. |

**Table 52 Reports of sudden death among quetiapine patients enrolled in clinical studies in Alzheimer's disease [a]**

| Patient identification number | Age/ sex | Indication/Daily dose (mg)/Time to event [b] | Preferred terms in database relevant to outcome of death | Clinical information | Comments [c] |
|---|---|---|---|---|---|
| 1999UW00243 | 76/F | Alzheimer's disease/100/75 days | Cardio-respiratory arrest | Medical history included arteriosclerotic heart disease, diabetes mellitus, organic brain syndrome, schizophrenia. Medications included insulin, glyburide, digoxin, potassium, furosemide. Brought to the emergency room with discomfort, clammy skin, restlessness. Suffered cardiac arrest and could not be resuscitated. | Adjudicated by external reviewer as a case of sudden death. |
| 1996AP18864 | 81/F | Alzheimer's disease / 75 /6 months | Cardio-respiratory arrest | Medical history included hypertension, migraine headaches, bilateral cataracts, pneumonia, urinary tract infections, and osteoarthritis. Concurrent medications included trazodone and cyproheptadine; prior hydrochlorothiazide and diltiazem. While dancing, she suddenly began to gasp for air and was pronounced dead shortly thereafter. | Adjudicated by external reviewer as a case of sudden death. |
| 1998AP46349 | 78/M | Alzheimer's disease/200/130 days | Cardiac Arrest | History includes epilepsy, CHF, AF, bronchitis. Medications include primidone, salbutamol, phenytoin, verapamil. Died due to cardiac arrest and acute respiratory failure. | Adjudicated by external reviewer as a case of sudden death. |
| 1999UW02597 | 74/F | Alzheimer's disease/600/38 days | Urosepsis | Medical history includes akathisia, hypertension, hip fracture, history of thoracotomy, osteoporosis. Medications include carbamazepine, nystatin, amoxicillin, potassium, prochlorperazine. Treated with Compazine and antibiotics for vomiting and presumed urosepsis. Quetiapine and carbamazepine withheld for 48 hours due to vomiting. Patient fell climbing out of bed | Adjudicated by external reviewer as a case of sudden death. Reviewer comment: Cause of death urosepsis but death sudden. |

**Table 52 Reports of sudden death among quetiapine patients enrolled in clinical studies in Alzheimer's disease [a]**

| Patient identification number | Age/ sex | Indication/Daily dose (mg)/Time to event [b] | Preferred terms in database relevant to outcome of death | Clinical information | Comments [c] |
|---|---|---|---|---|---|
| | | | | (sustaining a broken nose and lacerations). Later that day found dead in bed with cause of death reported as urosepsis. | |
| 2002UW16676 | 96/F | Alzheimer's disease/200/1 day | Arrhythmia | History of hypertension, CAD, CHF, AF. Medications included levothyroxine, diltiazem, methenamine, morphine. Found unresponsive with labored breathing. Comfort measures provided due to DNR status and patient expired. Cause of death reported as arrhythmia due to CAD. No autopsy. | Adjudicated by external reviewer as a case of sudden death. |
| 2003UW03807 | 93/F | Alzheimer's disease/200/37 days | MI | History included CHF, hypothyroidism, agitation, hypertension, MI, CAD. Medications included furosemide, potassium, digoxin, levothyroxine, trazodone, metoprolol, pantoprazole, lisinopril, ipratropium. Patient passed out, was assisted back to bed, and died. No resuscitation as the patient had DNR status. Cause of death presumed to be "MI secondary to CAD". | Adjudicated by external reviewer as a case of sudden death. Reviewer comment: Witnessed arrest, DNR order. |

[a] As discussed in Section 4.4.6.1, the clinical and safety databases were searched for terms describing events mapping to the preferred terms of "sudden death", "sudden cardiac death", "cardiac death", "cardiac arrest", and "cardio-respiratory arrest". Cases in this table that map to other preferred terms were identified by external expert review as described in Section 4.4.6.2.

[b] Patient being treated with quetiapine at time of event unless otherwise indicated.

[c] Although adjudicated by external reviewer NOT to be a case of sudden death, the narrative is included for completeness, as the investigator commented on a cardiac-related issue.

AF Atrial fibrillation. BP Blood pressure. CAD Coronary artery disease. CHF Congestive heart failure. DNR Do not resuscitate. ECG Electrocardiogram. MI Myocardial infarction. PVD Peripheral vascular disease.

**Table 53 Seventeen patients – to be adjudicated [a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy) [b] | Preferred terms in database relevant to outcome of death | Clinical information | Comments |
|---|---|---|---|---|---|
| **Quetiapine** | | | | | |
| 1995AP08707 | 46/M | Schizophrenia/250 mg/treated 65 days (last dose 11 weeks prior to death) | Completed suicide | Pt committed suicide 11 wks after stopping study therapy | |
| 1995AP12330 | 81/M | Alzheimer's dementia/25-50/treated 15 days (last dose 32 days prior to death) | Pneumonia (not fatal)<br>Reported in narrative that Pt died (cause not provided) | Hx of insomnia, athralgia, arthritis, delusions, peptic ulcer, spinal laminectomy, hernia treated w/ ranitidine, ibuprofen, trazodone, prochlorperazine. Pt withdrawn from study d/t LOE. Pt developed pneumonia 8 days after study tx d/c'd. 24 days later reported that Pt died & that COD was not related to quetiapine or pneumonia. | |
| 1996AP18174 | 70/M | Parkinson's disease, dementia, schizophrenia/25-100/treated 166 days (last dose two months prior to death) | CVA, dehydration, normal pressure hydrocephalus (all not fatal)<br>Pt died (cause not provided) | Hx of hernia repair, sinus arrhythmia, spinal laminectomy, nephrectomy, joint arthroplasty treated w/ lanoxin. Pt had CVA, dehydration, normal pressure hydrocephalus on Day 166 of therapy w/ quetiapine. CVA & dehydration resolved by next day. Quetiapine d/c'd sometime the following month. Reported that Pt died 2 mos after quetiapine was d/c'd. COD was not provided. | |
| 1997AP32589 | 70/M | Dementia/25-100/treated 530 days (last dose 7 days prior to death) | MI | Hx of unspecified cardiovascular disease, cardiac arrhythmia, Parkinson's disease, insomnia, hallucination, incontinence, senile dementia treated w/ dipyridamole, trazodone, multi-vit, carbidopa/levodopa, ASA. On day 530 of therapy Pt hospitalized for dehydration. Quetiapine & all other meds d/c'd, Tx=IVF. Pt back to nursing home next day w/ order for only comfort measures. One wk later Pt had MI & died. | |

**Table 53 Seventeen patients – to be adjudicated [a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy) [b] | Preferred terms in database relevant to outcome of death | Clinical information | Comments |
|---|---|---|---|---|---|
| 1998AP44067 | 56/M | Schizophrenia/800/treated 108 days (last dose 21 days prior to death) | Hepatic neoplasm malignant | Day 108 Pt hospitalized w/ severe hepatomegaly, c/o wt loss, worsening anemia, SOB, dizziness, ankle edema, raised platelet count. Initial dx=heart failure. Abdominal US=confirmed hepatomegaly d/t liver malignancy & excluded heart failure. Pt d/c'd from study 6 d later. Pt died 3 wks later from liver carcinoma. | |
| 1998AP44781 | 63/M | Schizophrenia/75-300/ 244 days | Pneumonia | Hx of DM & HTN. Day 244 Pt developed fever (38°C). Tx w/ abx. Temp fell to 37.1°C next day. 4 days later Temp=39.4°C. CXR=abnormalities in R upper lung & L middle lobe. 2 days later Pt temp normal but condition worsened & became cyanotic. Resuscitation attempted but unsuccessful. COD=pneumonia probably d/t influenza (since abx were unsuccessful). | |
| 1998AP48378 | 91/F | Alzheimer's dementia/Unk dose/treated 4 days (last dose 2 wks prior to death) | Constipation, fecaloma, confusional state (all not fatal)<br>COD reported as heart failure | Hx of CHF, atrial fibrillation, coagulopathy, arthritis, depression, COPD treated w/ enalapril, lanoxin, furosemide, coumadin, lofepramine, beclomethasone, acetaminophen/codeine. One wk prior to starting tx Pt had elevated total bilirubin, ALP, neutrophils & low TSH, lymphocytes, eosinophils. Also ECG=RBBB, widespread ST depression, T-wave inversion, compatible w/ ischemia. After 4 days on tx Pt had severe constipation, fecal impaction, toxic confusional state. Pt hospitalized & withdrawn from study. 2 wks later Pt died, COD=heart failure. At time of death events of constipation, fecal impaction, & confusion were ongoing. | |

**Table 53 Seventeen patients – to be adjudicated [a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy) [b] | Preferred terms in database relevant to outcome of death | Clinical information | Comments |
|---|---|---|---|---|---|
| 2000AP02582 | 66/F | Alzheimer's dementia, schizophrenia/400/treated 652 days (last dose 48 days prior to death) | Pulmonary embolism, Anemia, Hypoxia | Pt started risperidone 3 wks after quetiapine d/c'd & contd x 10 days. 16 days after risperidone d/c'd (48 days after last dose of quetiapine) Pt died from PE. | |
| 2000AP02583 | 36/M | Schizophrenia/400/treated 32 days (last dose 297 days prior to death) | Completed suicide | Hx of occasional cannabis use. Pt committed suicide on railway line more than 9 mos after quetiapine d/c'd. | |
| 2003SE01298 | 89/M | Alzheimer's disease, behavior disorder/400/67 days | Death (reported as d/t metastasis & terminal phase of cancer) | Hx of depression, constipation, urinary incontinence, prostate cancer, osteoporosis, folate deficiency, inguinal hernia, bone metastasis, arrhythmia, glaucoma treated w/ sertraline, Echinacea extract, flutamide, colecalciferol, sodium picosulfate. Pt died after 67 days of treatment d/t deterioration of general condition (metastases & terminal phase of cancer). | |
| 2003UW05862 | 89/F | Dementia/200/treated 2 wks (last dose 18 days prior to death | Mental status changes | Hx of pain, constipation, aortic stenosis, CVA, CAD, GERD, compression fracture treated w/ morphine, propranolol, verapamil, metoclopramide, acetaminophen, clopidogrel, captopril. 5 days after study tx d/t LOE Pt found unresponsive. Hospitalized d/t increasing altered mental status. Suspicion of UTI & dehydration noted. Pt rehydrated but status did not improve. Pt deteriorated & could not take fluids or food by mouth. Family opted against aggressive treatment. Pt died 13 days after onset of symptoms (18 days after last dose of quetiapine. No one cause of death noted. Investigator site learned of death from obituary. Death certificate listed cardiopulmonary arrest. | |

**Table 53 Seventeen patients – to be adjudicated [a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy) [b] | Preferred terms in database relevant to outcome of death | Clinical information | Comments |
|---|---|---|---|---|---|
| **Comparators** | | | | | |
| 1997AP31529 Haloperidol | 25/M | Schizophrenia/dose unspecified/treated 29 days (last dose 98 days prior to death) | Completed suicide | After 29 days of tx Pt withdrawn from study d/t muscle rigidity, tremor, syncope. Pt had a cold during time. After stopping study Pt started thioridazine and zuclopenthixol. 98 days after stopping study Pt committed suicide by hanging. | |
| 1996AP23657 Haloperidol | 27/F | Schizophrenia/dose unspecified/treated 57 days in blinded study & contd haloperidol x 28 days | Completed suicide | Hx of suicide attempt. Treated w/ senna, biperiden, brotizolam, estazalom. Pt finished study and contd treatment w/ haloperidol. After 86 days total of haloperidol Pt committed suicide. | |
| 1997AP31350 Haloperidol | 40/M | Schizophrenia/1.5-9/46 days | Convulsion, Subdural hematoma, Water intoxciation | Hx of Parkinsonism, water intoxication but had not had a seizure for some time. After 46 days of study tx Pt found dead. Investigator suspected Pt may have had seizure d/t water intoxication, fallen & sustained a subdural hametoma which caused death. | |
| 1998UW49570 Risperidone | 21/M | Schizophrenia/5/173 days | Completed suicide | After 173 day treatment Pt committed suicide by hanging. | |
| **Placebo** | | | | | |

**Table 53 Seventeen patients – to be adjudicated [a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy) [b] | Preferred terms in database relevant to outcome of death | Clinical information | Comments |
|---|---|---|---|---|---|
| 2003UW16748 Placebo | 81/M | Dementia/69 days (last dose 16 days prior) | Renal failure | Hx of chronic renal insufficiency, HTN, CAD, MI, atrial fibrillation, CHF, COPD. Treated w/ milk of magnesia, guaifenesin, levofloxacin, metamucil, warfarin, cetirizine, donepezil, paracetamol, bisacodyl, lactenix, furosemide, lansoprazole, metoprolol, pravastatin, prednisone, digoxin. 16 days after study Pt hospitalized w/ renal failure w/ clinical anasarca & nephrotic syndrome. Lab assessments, during hospitalization, yielded abnormal BUN, creatinine. 4 days later Pt died. COD=hypoxia d/t acute respiratory failure complicated by nephrotic syndrome. | |

**Table 53 Seventeen patients – to be adjudicated [a]**

| Patient ID | Age/ sex | Indication/daily dose (mg)/time to event (from start of therapy) [b] | Preferred terms in database relevant to outcome of death | Clinical information | Comments |
|---|---|---|---|---|---|
| 2003UW10461<br>Placebo | 81/M | Dementia/16 days (last dose 33 days prior to death) | Bradycardia, Hematuria (both non-fatal)<br>Reported as death cause unknown in narrative | Hx of HTN, hyperlipidemia, cerebrovascular insufficiency, malnourishment, abnormal LFTs, UTI, normocytic anemia, dehydration w/ heat stroke, Alzheimer's dementia & psychosis. Treated w/ gatifloxacin, albuterol, temazepam, olanzapine, donepezil; for the treatment of pneumonia, insomnia, psychosis, and dementia respectively. 2 wks after starting trial therapy, Pt was alert & cooperative 1 hour later, Pt somnolent, difficult to arouse, &in an unresponsive state. HR=40 bpm. Tx=atropine by rescue squad. Pt became awake & returned to baseline mental status. ECG=sinus bradycardia w/ premature atrial complexes. Pt pulled his Foley catheter out in ER & began having a large amount of gross hematuria. Pt hospitalized & treated for 3 days before being discharged to the rehab. Pt d/c'd from study d/t events. Pt later died in the rehabilitation center 33 days after study tx stopped. COD unknown. | |

[a] As discussed in Section 4.4.6.1, the clinical and safety databases were searched for terms describing events mapping to the preferred terms of "sudden death", "sudden cardiac death", "cardiac death", "cardiac arrest", and "cardio-respiratory arrest". Cases in this table are events leading to death that map to preferred terms OTHER than the ones described above.

[b] Patient being treated with quetiapine or comparator at time of event unless otherwise indicated in parentheses.
Abbreviations: Blood Pressure (BP); Cardiopulmonary Resuscitation (CPR); Electrocardiogram (ECG); Intensive Care Unit (ICU); Myocardial Infarction (MI); abx (antibiotics); PE (pulmonary embolism); RBBB (right bundle branch block); COD (cause of death); CAD Coronary artery disease. CHF Congestive heart failure; COPD (chronic obstructive pulmonary disease); SOB (shortness of breath); CXR (chest xray); HTN (hypertension); GERD (gastroesophageal reflex disease); DM (diabetes mellitus); IVF (intravenous fluids); UTI (urinary tract infection); CVA (cerebral vascular accident)

## Appendix D2 Detailed results of Pfizer Study 54

This study, performed by Pfizer and designed with FDA input, examined the effects of ziprasidone as well as haloperidol, thioridazine, olanzapine, risperidone, and quetiapine. Haloperidol was not expected to increase the QTc interval, but there was no placebo control. The study also included a phase in which a metabolic inhibitor was added to each drug to determine additive effects on the QTc interval under conditions of maximum inhibition of clearance. Patients randomized to quetiapine were titrated to a maximum dose of 375 mg twice daily and received ketoconazole 400 mg twice daily during the metabolic inhibition phase of the study. QTc was measured by several techniques.

There were 127 patients enrolled in the study. Mean $C_{max}$ plasma concentrations increased in all groups after the addition of a metabolic inhibitor; the increase was greatest for quetiapine. Each agent studied was associated with measurable QTc prolongation at steady-state peak plasma concentrations which was not augmented by metabolic inhibition.

Twenty-seven patients received quetiapine. In the absence of metabolic inhibition, patients treated with quetiapine had an increase in heart rate of 11.2 beats per minute (bpm), a decrease in uncorrected QT of 12.2 ms, an increase in QT interval corrected for heart rate using Bazett's formula (QTcB, Gordon 2000) of 14.5 ms and an increase in QTcF of 4.5 ms. In comparison, the mean QTcF increase from baseline for haloperidol (which was not expected to increase the QTc based on prior data) was 7.1 msec.

Electrocardiogram data for all treatment groups are shown in Table 54.

**Table 54 Effect of different correction factors on mean $QT_c$ change from baseline; Study 054 Period 3 (inhibitor absent)[a]**

| | Ziprasidone | Risperidone 6-8 mg/16 mg | Olanzapine | Quetiapine | Thioridazine | Haloperidol |
|---|---|---|---|---|---|---|
| QT interval (msec)<br>Heart rate (bpm) | 6.8<br>4.6 | –12.1/–8.0<br>9.5/6.4 | –8.9<br>6.5 | –12.2<br>11.2 | 18.7<br>5.7 | 12.5<br>–2.9 |
| Log-linear QT corrections $(QT*RR)^{-k}$ | | | | | | |
| Bazett (k=0.5) | 20.3 | 11.6/9.1 | 6.8 | 14.5 | 35.6 | 4.7 |
| FDA-proposed (k=0.37) | 16.5 | 4.9/4.3 | 2.3 | 6.9 | 30.8 | 6.8 |
| Baseline 054 data (k=0.35)[b] | 15.9 | 3.9/3.6 | 1.7 | 5.7 | 30.1 | 7.1 |
| Fridericia (k=0.33) | 15.5 | 3.1/3.0 | 1.1 | 4.8 | 29.6 | 7.3 |
| Linear QT corrections (QT+k(1000–RR)) | | | | | | |
| Hodges | 14.9 | 4.5/3.3 | 2.5 | 7.5 | 28.7 | 7.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| (QT+1.75(HR–60) | | | | | | |
| Framingham (k=0.154) | 14.9 | 3.6/3.7 | 1.6 | 4.4 | 28.5 | 6.1 |
| Baseline 054 data (k=0.148)[b] | 14.6 | 3.0/3.3 | 1.2 | 3.8 | 28.1 | 6.3 |

a Data for patients who completed the study.
b Derived from regression on baseline data from Study 054.

In quetiapine-treated patients, QTc prolongation was not significantly augmented with ketoconazole. Electrocardiogram data for all treatment groups in the presence of the metabolic inhibitor are shown in Table 55.

**Table 55 Effect of different correction factors on mean $QT_c$ change from baseline; Study 054 Period 4 (inhibitor present)[a]**

| | Ziprasidone | Risperidone 16 mg | Olanzapine | Quetiapine | Thioridazine | Haloperidol |
|---|---|---|---|---|---|---|
| QT interval (msec)<br>Heart rate (bpm) | 10.0<br>3.6 | 1.1<br>0.5 | –1.8<br>3.0 | –15.8<br>15.1 | 33.3<br>–2.1 | 22.5<br>–5.7 |
| Log-linear QT corrections $(QT*RR)^{-k}$ | | | | | | |
| Bazett (k=0.5) | 20.0 | 3.2 | 5.3 | 19.7 | 28.0 | 8.9 |
| FDA-proposed (k=0.37) | 17.0 | 2.7 | 3.3 | 9.5 | 29.3 | 12.8 |
| Baseline 054 data (k=0.35)[b] | 16.6 | 2.6 | 3.0 | 8.0 | 29.6 | 13.3 |
| Fridericia (k=0.33) | 16.3 | 2.5 | 2.8 | 6.7 | 29.7 | 13.8 |
| Linear QT corrections (QT+k(1000–RR)) | | | | | | |
| Hodges (QT+1.75(HR–60) | 16.3 | 2.0 | 3.4 | 10.6 | 29.6 | 12.5 |
| Framingham (k=0.154) | 15.5 | 2.5 | 2.8 | 5.9 | 28.6 | 12.8 |
| Baseline 054 data (k=0.148)[b] | 15.3 | 2.4 | 2.6 | 5.1 | 28.8 | 13.1 |

a Data for patients who completed the study.
b Derived from regression on baseline data from Study 054.
bpm Beats per minute. msec Milliseconds.

Based on data from previous clinical studies, haloperidol was expected to have little or no effect on the QTc interval, while thioridazine was expected to have the greatest effect. Thioridazine is a classic antipsychotic drug that has recently been shown to be associated with an increased risk of torsade de pointes, and it has been re-labeled by the FDA. However, Pfizer noted that the duration of the QTc interval was dependent upon the heart rate correction used. When the Bazett formula is used, the effects of drugs associated with an increase in heart rate (eg, quetiapine) are maximized, while the effects of drugs that lower the heart rate (eg, haloperidol) are minimized (Gordon 2000). QTcF is considered a more reliable method than QTcB for assessing the QTc effects of drugs that also increase the heart rate (FDA ICH E14 Guidance 2005).

Upon reviewing the results of Study 054, the FDA made the following remarks, quoted directly:

> *"In summarizing the results of Study 054, Pfizer has stated that this study reveals an effect on QTc prolongation [during ziprasidone administration] approximately 10 ms greater than that observed with 4 of the comparison drugs (ie, haloperidol, olanzapine, risperidone, and quetiapine), and an effect on QTc prolongation approximately 10 ms less than that observed with thioridazine.*
>
> *Regarding the increases from baseline observed for the other drugs in Study 054, it is not clear, in our view, whether the observed QTc increases represent actual drug-related effects or represent placebo effect, since we have an abundance of data from multiple independent development programs showing no difference between haloperidol (at the oral dose used in Study 054) and placebo on QTc.*
>
> *In particular, the critical safety question will be the relevance of the 10 ms prolongation of the QTc observed for ziprasidone, and **not** [emphasis added] for several other antipsychotic drugs included in Study 054, for the approvability of this drug."*

In this prospective, comparative study performed by Pfizer and designed with FDA input, the effects of quetiapine were studied over a range of individual plasma concentrations that varied by 2 orders of magnitude, from approximately $10^2$ ng/mL to approximately $10^4$ ng/mL (Gordon 2000). All the correction formulas applied to the data, with the exception of the Bazett formula (known to overestimate the QTc interval when the heart rate is increased), confirmed that the change in QTc interval during quetiapine treatment was no greater than the change during haloperidol treatment.

# Appendix E US Product Information for Seroquel

## 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.***

- **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)**

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

BOXED WARNING, Increased Mortality in Elderly Patients With Dementia, 08/2008
Warnings and Precautions, Increased Mortality in Elderly Patients With Dementia-Related Psychosis (5.1), 08/2008
Indications and Usage, Bipolar Disorder (1.2), 10/2008
Dosage and Administration, Bipolar Disorder (2.2), 10/2008
Warnings and Precautions, Hyperglycemia (5.3), 01/2009
Warnings and Precautions, Hyperlipidemia (5.4), 01/2009
Warnings and Precautions, Weight Gain (5.5), 01/2009
Warnings and Precautions, Hypothyroidism (5.12), 01/2009
Warnings and Precautions, Hyperprolactinemia (5.13), 01/2009
Warnings and Precautions, Increases in Blood Pressure (Children and Adolescents) (5.14), 01/2009
Adverse Reactions (6.1), 01/2009

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

SEROQUEL XR is an atypical antipsychotic agent indicated for the treatment of:

- Schizophrenia (1.1)
- Bipolar Disorder (1.2)
  - depressive episodes associated with bipolar disorder
  - manic or mixed episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex
  - maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex

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

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)

**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. (2.1)

**Bipolar Depression**: Usual Dose for Acute Treatment - administer once daily in the evening starting with 50 mg per day and increasing doses to reach 300 mg per day by day 4 (2.2)

**Bipolar Mania**: Usual Dose for Acute Monotherapy or Adjunct Therapy (with lithium or divalproex) - administer once daily in the evening starting with 300 mg on day 1, 600 mg on day 2 and adjust between 400 mg – 800 mg per day thereafter depending on the clinical response and tolerance of the individual patient (2.2)

**Bipolar Maintenance:** Continue treatment at the dosage required to maintain symptom remission (2.2)

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

Extended-Release Tablets: 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg

**----------CONTRAINDICATIONS----------**

None

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

- **Increased Mortality in Elderly Patients with Dementia-Related Psychoses**: Antipsychotic drugs, including quetiapine, are associated with an increased risk of death; causes of death are variable. (5.1)
- **Suicidality and Antidepressant Drugs:** Increased the risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders. (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)
- **Hyperlipidemia:** Increases in cholesterol and triglycerides have been reported in clinical trials. (5.4)
- **Weight Gain:** Weight gain has been reported in clinical trials. (5.5)
- **Neuroleptic Malignant Syndrome (NMS):** Manage with immediate discontinuation and close monitoring. (5.6)
- **Tardive Dyskinesia:** Discontinue if clinically appropriate. (5.7)
- **Orthostatic Hypotension**: Associated dizziness, tachycardia and syncope especially during the initial dose titration period. Use in caution in patients with known cardiovascular or cerebrovascular disease. (5.8)
- **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. (5.9)
- **Cataracts:** Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination should be done when starting treatment and at 6-month intervals during chronic treatment. (5.10)
- **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high risk patients should accompany drug therapy. (5.20)
- See Full Prescribing Information for additional **WARNINGS and PRECAUTIONS**.

**---------- ADVERSE REACTIONS----------**

Most common adverse reactions (incidence ≥5% and twice placebo) are somnolence, dry mouth, hyperlipidemia, constipation, dyspepsia, dizziness, orthostatic hypotension, weightgain, increased appetite, fatigue, hyperglycemia, dysarthria and nasal congestion. (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**: Consider a lower starting dose (50 mg/day), slower titration, and careful monitoring during the initial dosing period in the elderly. (2.3 and 8.5)
- **Hepatic Impairment**: Lower starting dose (50 mg/day) and slower titration may be needed. (2.3, 8.7, 12.3)
- **Pregnancy:** Limited human data. Based on animal data, may cause fetal harm. (8.1)
- **Nursing Mothers:** Caution should be exercised when administered to a nursing woman. (8.3)
- **Pediatric Use**: Safety and effectiveness have not been established. (8.4)

**SEE 17 FOR PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE**

**REVISED 01/2009**

**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 antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. SEROQUEL XR is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions* (5.1)].**

### 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 [see *Warnings and Precautions* (5.2)].**

# 1 INDICATIONS AND USAGE

## 1.1 Schizophrenia

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

The efficacy of SEROQUEL XR in schizophrenia was established, in part, on the basis of extrapolation from the established effectiveness of SEROQUEL [see *Clinical Studies* (14.1)].

## 1.2 Bipolar Disorder

SEROQUEL XR is indicated for the treatment of:

- acute depressive episodes associated with bipolar disorder
- acute manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or divalproex therapy and
- maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex

The efficacy of SEROQUEL XR in bipolar disorder was established, in part, on the basis of extrapolation from the established effectiveness of SEROQUEL [see *Clinical Studies* (14.2)].

# 2 DOSAGE AND ADMINISTRATION

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)].

## 2.1 Schizophrenia

### Usual Dose for Acute Treatment

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* (14.1)]. 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.

### 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 schizophrenia 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)].

## 2.2 Bipolar Disorder

### *Depressive Episodes Associated with Bipolar Disorder*

### Usual Dose for Acute Treatment

SEROQUEL XR should be administered once daily in the evening to reach 300 mg/day by Day 4.

Recommended Dosing Schedule

| Day | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|
| SEROQUEL XR | 50 mg | 100 mg | 200 mg | 300 mg |

### *Bipolar Mania*

### Usual Dose for Acute Monotherapy or Adjunct Therapy (with lithium or divalproex)

SEROQUEL XR should be administered once daily in the evening starting with 300 mg on Day 1 and 600 mg on Day 2. SEROQUEL XR can be adjusted between 400 mg and 800 mg beginning on Day 3 depending on the response and tolerance of the individual patient.

**Recommended Dosing Schedule**

| Day | Day 1 | Day 2 | Day 3 |
|---|---|---|---|
| SEROQUEL XR | 300 mg | 600 mg | 400 mg to 800 mg |

### Maintenance Treatment for Bipolar Disorder

While there is no body of evidence available to specifically address how long the patient treated with SEROQUEL XR

should remain on it, maintenance of efficacy in Bipolar I Disorder was demonstrated with SEROQUEL (administered twice daily totaling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase [see *Clinical Studies* (14.2)]. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [see *Clinical Studies* (14.2)].

## 2.3 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, 8.7) and *Clinical Pharmacology* (12)]. When indicated, dose escalation should be performed with caution in these patients.

Elderly patients should be started on SEROQUEL XR 50 mg/day and the dose can be increased in increments of 50 mg/day depending on the response and tolerance of the individual patient.

Patients with hepatic impairment should be started on SEROQUEL XR 50 mg/day. The dose can be increased daily in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerance 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* (7.1)].

## 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

Patients who are currently being treated with SEROQUEL (immediate release formulation) 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 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, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients 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

50 mg extended-release tablets
150 mg extended-release tablets
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 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 healthcare 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.

## 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. 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.

*Adults*: In 2 long-term placebo-controlled randomized withdrawal clinical trials for bipolar maintenance, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the mean change in glucose from baseline was +5.0 mg/dL for quetiapine and –0.05 mg/dL for placebo. The exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dL) for patients more than 8 hours since a meal (however, some patients may not have been precluded from calorie intake from fluids during fasting period) was 18.0 per 100 patient years for SEROQUEL (10.7% of patients; n=556) and 9.5 for placebo per 100 patient years (4.6% of patients; n=581).

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with quetiapine 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. The mean change in glucose from baseline was 2.70 mg/dL for quetiapine and 1.06 mg/dL 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%. The mean change in fasting glucose from baseline was 3.2 mg/dL and mean change in 2 hour glucose from baseline was -1.8 mg/dL for quetiapine.

*Children and Adolescents*: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In a placebo-controlled quetiapine monotherapy study of adolescent patients (13–17 years of age) with schizophrenia (6 weeks duration), the mean change in fasting glucose levels for SEROQUEL compared to placebo was –0.75 mg/dL versus –1.70 mg/dL. In a placebo-controlled SEROQUEL monotherapy study of children and adolescent patients (10–17 years of age) with bipolar mania (3 weeks duration), the mean change in fasting glucose level for quetiapine compared to placebo was 3.62 mg/dL versus –1.17 mg/dL. No patient in either study with a baseline normal fasting glucose level (<100 mg/dL) or a baseline borderline

fasting glucose level (≥100 mg/dL and <126 mg/dL) had a treatment-emergent blood glucose level of ≥126 mg/dL.

## 5.4 Hyperlipidemia

*Adults*: In clinical trials with SEROQUEL XR the percentage of patients with the following changes in cholesterol and triglycerides have been reported [see *Adverse Reactions* (6.3)].

**Percentage of Patients with Shifts from Normal Baseline to Clinically Significant Levels**

| | Cholesterol ≥ 240 mg/dL | Triglycerides ≥ 200 mg/dL |
|---|---|---|
| Schizophrenia (6 weeks duration) | | |
| SEROQUEL XR | 9% | 18% |
| Placebo | 9% | 5% |
| Bipolar Depression (8 weeks duration) | | |
| SEROQUEL XR | 7% | 8% |
| Placebo | 3% | 8% |
| Bipolar Mania (up to 12 weeks duration) | | |
| SEROQUEL XR | 7% | 15% |
| Placebo | 4% | 6% |

*Children and Adolescents*:
Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In clinical trials with SEROQUEL the percentage of patients with the following changes in cholesterol and triglycerides have been reported.

**Percentage of Patients with Shifts from Normal Baseline to Clinically Significant Levels**

| | Cholesterol ≥ 240 mg/dL | Triglycerides ≥ 200 mg/dL |
|---|---|---|
| Schizophrenia (13-17 years, 6 weeks duration) | | |
| SEROQUEL | 12% | 17% |
| Placebo | 2% | 8% |

| Bipolar Mania (10-17 years, 3 weeks duration) | | |
|---|---|---|
| SEROQUEL | 10% | 22% |
| Placebo | 3% | 13% |

## 5.5 Weight Gain

*Adults*: In clinical trials with SEROQUEL XR the following increases in weight have been reported.

**Proportion of Patients with Weight Gain ≥7% of Body Weight (Adults)**

| | Schizophrenia (up to 6 weeks) | Bipolar Mania (up to 12 weeks) | Bipolar Depression (up to 8 weeks) |
|---|---|---|---|
| SEROQUEL XR | 10% | 5.1% | 8.2% |
| Placebo | 5% | 0% | 0.8% |

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%).

*Children and Adolescents*: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In two clinical trials with SEROQUEL, one in bipolar mania and one in schizophrenia, reported increases in weight are included in the table below. When treating pediatric patients with SEROQUEL XR for any indication, weight gain should be assessed against that expected for normal growth. The mean change in body weight in the schizophrenia trial was 2.0 kg in the SEROQUEL group and -0.4 kg in the placebo group and in the bipolar mania trial it was 1.7 kg in the SEROQUEL group and 0.4 kg in the placebo group.

**Proportion of Patients with Weight Gain ≥7% of Body Weight (Children and Adolescents)**

| | Schizophrenia (6 weeks duration) | Bipolar Mania (3 weeks duration) |
|---|---|---|
| SEROQUEL | 21% | 12% |
| Placebo | 7% | 0% |

In an open-label study that enrolled patients from the above two pediatric trials, 63% of patients (241/380) completed 26 weeks of therapy with SEROQUEL. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients gained $\geq$ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on SEROQUEL met this criterion after 26 weeks of treatment.

## 5.6 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.

## 5.7 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs including quetiapine. 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 XR 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 XR, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome.

## 5.8 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 ά1-adrenergic antagonist properties. Syncope was reported in 0.3% (4/1239) of the patients treated with SEROQUEL XR, compared with 0.3% (2/619) on placebo. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) on placebo. Orthostatic hypotension, dizziness, and syncope may lead to falls.

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.

## 5.9 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 XR. 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)].

## 5.10 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.

## 5.11 Seizures

During clinical trials with SEROQUEL XR, seizures occurred in 0.1% (1/1239) of patients treated with SEROQUEL XR compared to 0.5% (3/619) on placebo. During clinical trials with SEROQUEL, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo. As with other antipsychotics, quetiapine fumarate 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.

## 5.12 Hypothyroidism

*Adults*: 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 0.7% (26/3489) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of these patients with TSH increases needed replacement thyroid treatment.

*Children and Adolescents*: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts to potentially clinically important thyroid function values at any time for SEROQUEL treated patients and placebo-treated patients for elevated TSH was 2.9% vs 0.7%, respectively and for decreased total thyroxine was 2.8% vs

0%, respectively. Of the SEROQUEL treated patients with elevated TSH levels, 1 had simultaneous low free T4 level at end of treatment.

## 5.13 Hyperprolactinemia

*Adults*: During clinical trials with quetiapine, the incidence of shifts in prolactin levels to a clinically significant value occurred in 3.6% (158/4416) of patients treated with quetiapine compared to 2.6% (51/1968) on placebo.

*Children and Adolescents*: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts in prolactin levels to a clinically significant value (>20 µg/L males; > 26 µg/L females at any time) was 13.4% for SEROQUEL compared to 4% for placebo in males and 8.7% for SEROQUEL compared to 0% for placebo in females.

Like other drugs that antagonize dopamine D2 receptors, SEROQUEL XR elevates prolactin levels in some patients and the elevation may persist during chronic administration. Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

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 considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in carcinogenicity studies conducted in mice and rats. 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, but the available evidence

is too limited to be conclusive [see *Carcinogenesis, Mutagenesis, Impairment of Fertility* (13.1)].

### 5.14 Increases in Blood Pressure (Children and Adolescents)

Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescents with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increases at any time in systolic blood pressure (≥20 mmHg) was 15.2% for SEROQUEL and 5.5% for placebo; the incidence of increases at any time in diastolic blood pressure (≥10 mmHg) was 40.6% for SEROQUEL and 24.5% for placebo.

### 5.15 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 placebo-controlled trials ranged between 1% and 2% 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 quetiapine.

### 5.16 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 was reported in 24.7% of patients on SEROQUEL XR compared to 10.3% of placebo patients. In a bipolar depression clinical trial, somnolence was reported in 51.8% of patients on SEROQUEL XR compared to 12.9% of placebo patients. In a clinical trial for bipolar mania, somnolence was reported in 50.3% of patients on SEROQUEL XR compared to 11.9% 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. Somnolence may lead to falls.

### 5.17 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.

### 5.18 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.

### 5.19 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.

### 5.20 Suicide

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder; 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 was 0.6% in SEROQUEL XR treated patients and 0.9% in placebo-treated patients.

In an 8-week clinical study in patients with bipolar depression (N=137 for SEROQUEL XR and 140 for placebo), the incidence of treatment emergent suicidal ideation or suicide attempt was 0.7% for SEROQUEL XR treated patients and 1.4% for placebo.

In a 3-week clinical study in patients with bipolar mania (N=311, 151 for SEROQUEL XR and 160 for placebo), the incidence of treatment emergent suicidal ideation or suicide attempt was 1.3% for SEROQUEL XR compared to 3.8% for placebo.

### 5.21 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* (5.8)].

### 5. 22 Withdrawal

Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including quetiapine fumarate. 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 1239 patients exposed to SEROQUEL XR for the treatment of schizophrenia and bipolar disorder in placebo controlled trials. This experience corresponds to approximately 143.1 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 schizophrenia trials. In a single clinical trial in patients with bipolar depression, 13% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 4% on placebo. In a single clinical trial in patients with bipolar mania, 4.6% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 8.1% on placebo.

### 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[1]**

| **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** | | |
| Somnolence[2] | 25% | 10% |
| 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.
[2]Somnolence combines adverse reaction terms somnolence and sedation.

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 somnolence (25%), dry mouth (12%), dizziness (10%), and dyspepsia (5%).

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of bipolar depression (up to 8 weeks) in ≥ 5% patients treated with SEROQUEL XR 300 mg/day where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

**Table 3. Treatment-Emergent Adverse Reactions in an 8-Week Placebo-Controlled Clinical Trial for the Treatment of Bipolar Depression[1]**

| **Body System/Preferred Term** | **SEROQUEL XR (n=137)** | **PLACEBO (n=140)** |
|---|---|---|
| **Gastrointestinal Disorders** | | |
| Dry Mouth | 37% | 7% |
| Constipation | 8% | 6% |
| Dyspepsia | 7% | 1% |
| **General Disorders and Administration Site Conditions** | | |
| Fatigue | 6% | 2% |

| | | |
|---|---|---|
| **Investigations** | | |
| Weight Gain | 7% | 1% |
| **Metabolism and Nutrition Disorder** | | |
| Increased Appetite | 12% | 6% |
| **Nervous System Disorders** | | |
| Somnolence[2] | 52% | 13% |
| Dizziness | 13% | 11% |

[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 and insomnia.
[2]Somnolence combines adverse reaction terms somnolence and sedation.

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 somnolence (52%), dry mouth (37%), increased appetite (12%), weight gain (7%), dyspepsia (7%), and fatigue (6%).

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of bipolar mania (up to 3 weeks) in ≥ 5% patients treated with SEROQUEL XR (doses ranging from 400 to 800 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

**Table 4: Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania[1]**

| **Body System/Preferred Term** | **SEROQUEL XR (n=151)** | **PLACEBO (n=160)** |
|---|---|---|
| **Gastrointestinal Disorders** | | |
| Dry Mouth | 34% | 7% |
| Constipation | 10% | 3% |
| Dyspepsia | 7% | 4% |

| | | |
|---|---|---|
| **General Disorders and Administration Site Conditions** | | |
| Fatigue | 7% | 4% |
| **Investigations** | | |
| Weight Gain | 7% | 1% |
| **Nervous System Disorders** | | |
| Somnolence[2] | 50% | 12% |
| Dizziness | 10% | 4% |
| Dysarthria | 5% | 0% |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Nasal Congestion | 5% | 1% |

[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.
[2]Somnolence combines adverse reaction terms somnolence and sedation.

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 somnolence (50%), dry mouth (34%), dizziness (10%), constipation (10%), weight gain (7%), dysarthria (5%), and nasal congestion (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-controlled 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 in clinical trials with quetiapine and not listed elsewhere in the label:
abnormal dreams and nightmares, peripheral edema, rhinitis, eosinophilia, hypersensitivity, elevations in gamma-GT levels, restless legs syndrome, and elevations in serum creatine phosphokinase (not associated with NMS).

Extrapyramidal Symptoms:

**Dystonia**

*Class Effect*: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

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.

*Adults*: In placebo-controlled clinical trials with quetiapine, utilizing doses up to 800 mg per day, the incidence of any adverse reactions potentially related to EPS ranged from 8% to 11% for quetiapine and 4% to 11% for placebo.

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.

In a placebo-controlled clinical trial for the treatment of bipolar depression utilizing 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 4.4% for SEROQUEL XR and 0.7% in the placebo group. In this study, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dystonia, hypertonia) did not exceed 1.5% for any individual adverse reaction.

In a placebo-controlled clinical trial for the treatment of bipolar mania, utilizing the dose range of 400-800 mg/day of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 6.6% for SEROQUEL XR and 3.8% in the placebo group. In this study, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dystonia, restlessness, and cogwheel rigidity) did not exceed 2.0% for any adverse reaction.

*Children and Adolescents*: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In a short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration), the aggregated incidence of extrapyramidal symptoms was 12.9% for SEROQUEL and 5.3% for placebo, though the incidence of the individual adverse events (eg, akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration), the aggregated incidence of extrapyramidal symptoms was 3.6% for SEROQUEL and 1.1% for placebo.

Increased Appetite

*Adults:* Data on increased appetite appear in Table 3 and in "Adverse Reactions that occurred in <5% of Patients" (both in this section).

*Children and Adolescents*: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increased appetite was 7.6% for SEROQUEL compared to 2.4% for placebo. In a 26-week open-label study that enrolled patients from the above two pediatric trials, the incidence of increased appetite was 10% for SEROQUEL.

## 6.2 Vital Signs and Laboratory Values

Hyperglycemia, hyperlipidemia, weight gain and orthostatic hypotension have been reported with quetiapine [see *Warnings and Precautions* (5.3, 5.4, 5.5 and 5.8)].

Neutrophil Counts

In three-arm SEROQUEL XR placebo-controlled monotherapy clinical trials, among patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of neutrophil count $<1.5 \times 10^9$/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 $<1.0 \times 10^9$/L among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine, 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* (5.9)].

ECG Changes:

3.9% of SEROQUEL XR patients, and 3.4% of 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 increase of 1 beat per minute for placebo.

This is consistent with the rates for 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* (5.8)].

### 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 includes anaphylactic reaction and galactorrhea.

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), Stevens-Johnson syndrome (SJS), and decreased platelets.

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

## 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 twice daily) and divalproex (500 mg twice daily) 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 twice daily) increased the oral clearance of quetiapine (300 mg twice daily) by 65%.

### Cimetidine

Administration of multiple daily doses of cimetidine (400 mg three times daily for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg three times daily). 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 twice daily), haloperidol (7.5 mg twice daily), or risperidone (3 mg twice daily) with quetiapine (300 mg twice daily) 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 three times daily 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 twice daily) was administered with quetiapine (150 mg twice daily). The mean oral clearance of total valproic acid (administered as divalproex 500 mg twice daily) was increased by 11% in the presence of quetiapine (150 mg twice daily). The changes were not significant.

### Lithium

Concomitant administration of quetiapine (250 mg three times daily) 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 three times daily 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:

There are no adequate and well-controlled studies of SEROQUEL XR use in pregnant women. In limited published literature, there were no major malformations associated with quetiapine exposure during pregnancy. In animal studies, embryo-fetal toxicity occurred. Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are limited published data on the use of quetiapine for treatment of schizophrenia and other psychiatric disorders during pregnancy. In a prospective observational study, 21 women exposed to quetiapine and other psychoactive medications during pregnancy delivered infants with no major malformations. Among 42 other infants born to pregnant women who used quetiapine during pregnancy, there were no major malformations reported (one study of 36 women, 6 case reports). Due to the limited number of exposed pregnancies,

these postmarketing data do not reliably estimate the frequency or absence of adverse outcomes.

When pregnant rats and rabbits were exposed to quetiapine during organogenesis, there was no increase in the incidence of major malformations in fetuses at doses up to 2.4 times the maximum recommended human dose for schizophrenia (MRHD, 800 mg/day on a mg/m$^2$ basis); however, there was evidence of embryo-fetal toxicity. In rats, delays in skeletal ossification occurred at 0.6 and 2.4 times the MRHD and in rabbits at 1.2 and 2.4 times the MRHD. At 2.4 times the MRHD, there was an increased incidence of carpal/tarsal flexure (minor soft tissue anomaly) in rabbit fetuses and decreased fetal weights in both species. Maternal toxicity (decreased body weights and/or death) occurred at 2.4 times the MRHD in rats and at 0.6-2.4 times the MRHD (all doses) in rabbits.

In a peri/postnatal reproductive study in rats, no drug-related effects were observed when pregnant dams were treated with quetiapine at doses 0.01, 0.12, and 0.24 times the MRHD. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 3.0 times the MRHD.

### 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 into human milk. Caution should be exercised when SEROQUEL XR is administered to a nursing woman.

In published case reports, the level of quetiapine in breast milk ranged from undetectable to 170 µg/L. The estimated infant dose ranged from 0.09% to 0.43% of the weight-adjusted maternal dose. Based on a limited number (N=8) of mother/infant pairs, calculated infant daily doses range from less than 0.01 mg/kg (at a maternal daily dose up to 100 mg quetiapine) to 0.1 mg/kg (at a maternal daily dose of 400 mg).

### 8.4 Pediatric Use

Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years [see *Warnings and Precautions* (5) and *Adverse Reactions* (6)].

### 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 *Dosing in Special Populations* (2.3) 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 *Dosage and Administration* (2.3) 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 behavior).

## 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)]. 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.

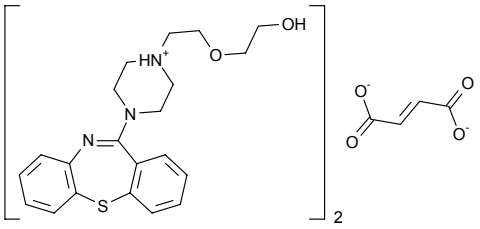
### 10.2 Management of Overdosage

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 $C_{42}H_{50}N_6O_4S_2 \bullet C_4H_4O_4$ 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 50 mg (peach), 150 mg (white), 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 (50, 200 and 300 mg tablets) are included in the film coating of specific strengths.

Each 50 mg tablet contains 58 mg of quetiapine fumarate equivalent to 50 mg quetiapine. Each 150 mg tablet contains 173 mg of quetiapine fumarate equivalent to 150 mg quetiapine. 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 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 ($5HT_2$) receptor antagonism, with the

metabolite N-desalkyl quetiapine (norquetiapine) having similar activity at $D_2$, but greater activity at $5HT2_A$ receptors, than the parent drug. Quetiapine's efficacy in bipolar depression may partly be explained by the high affinity and potent inhibitory effects that norquetiapine exhibits for the norepinephrine transporter.

Antagonism at receptors other than dopamine and serotonin with similar or greater affinities may explain some of the other effects of quetiapine and norquetiapine: antagonism at histamine $H_1$ receptors may explain the somnolence, antagonism at adrenergic $\alpha_1$b receptors may explain the orthostatic hypotension, and antagonism at muscarinic $M_1$ receptors may explain the anticholinergic effects.

## 12.2 Pharmacodynamics

Quetiapine and norquetiapine have affinity for multiple neurotransmitter receptors including dopamine $D_1$ and $D_2$, serotonin $5HT1_A$ and $5HT2_A$, histamine $H_1$, muscarinic, and adrenergic $\alpha_1$b and $\alpha_2$ receptors. Quetiapine differs from norquetiapine in having no appreciable affinity for muscarinic $M_1$ receptors whereas norquetiapine has high affinity. Quetiapine and norquetiapine lack appreciable affinity for benzodiazepine receptors.

**Receptor Affinities (Ki, nM) for Quetiapine and Norquetiapine**

| **Receptor** | **Quetiapine** | **Norquetiapine** |
|---|---|---|
| Dopamine $D_1$ | 428 | 99.8 |
| Dopamine $D_2$ | 626 | 489 |
| Serotonin $5HT1_A$ | 1040 | 191 |
| Serotonin $5HT2_A$ | 38 | 2.9 |
| Norepinephrine transporter | >10000 | 34.8 |
| Histamine $H_1$ | 4.41 | 1.15 |
| Adrenergic $\alpha_1$b | 14.6 | 46.4 |
| Adrenergic $\alpha_2$ | 617 | 1290 |

| | | |
|---|---|---|
| Muscarinic | 1086 | 38.3 |
| Benzodiazepine | >10000 | >10000 |

## 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 norquetiapine, 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 norquetiapine 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 approximately 12 hours for norquetiapine 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 norquetiapine.

### 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* (2.3)].

### 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* (2.3)].

### 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* (2.3)].

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 for schizophrenia and bipolar mania (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-year 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* (5.13)].

### 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.

## 14.2 Bipolar Disorder

### Depressive Episodes Associated with Bipolar Disorder

The efficacy of SEROQUEL XR for the acute treatment of depressive episodes associated with bipolar disorder in patients who met DSM-IV criteria for bipolar disorder was established in one 8-week, randomized, double-blind, placebo-controlled study (N=280 outpatients). This study included patients with bipolar I and II disorder, and those with and without a rapid cycling course. Patients randomized to SEROQUEL XR were administered 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3, and 300 mg on Day 4 and after.

The primary rating instrument used to assess depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 (no depressive features) to 60 (maximum score). The primary endpoint was the change from baseline in MADRS score at week 8. SEROQUEL XR was superior to placebo in reduction of MADRS score at week 8.

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 MADRS. 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 at week 8. 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).

### Bipolar Mania

The efficacy of SEROQUEL XR in the acute treatment of manic episodes was established in one 3-week, placebo-controlled trial in patients who met DSM-IV criteria for bipolar I disorder with manic or mixed episodes with or without psychotic features (N=316). Patients were hospitalized for a minimum of 4 days at randomization. Patients randomized to SEROQUEL XR received 300 mg on Day 1 and 600 mg on Day 2. Afterwards, the dose could be adjusted between 400 mg and 800 mg per day.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptoms in a range from 0 (no manic features) to 60 (maximum score). SEROQUEL XR was superior to placebo in the reduction of the YMRS total score at week 3.

The efficacy of SEROQUEL in the treatment of acute manic episodes was also 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 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 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 a 3-week placebo-controlled trial, 170 patients with acute bipolar mania (YMRS ≥ 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.

*Maintenance Therapy*
The efficacy of SEROQUEL in the maintenance treatment of Bipolar I Disorder was established in 2 placebo-controlled trials in patients (n=1326) who met DSM-IV criteria for Bipolar I Disorder. The trials included patients whose most recent episode was manic, depressed, or mixed, with or without psychotic features. In the open-label phase, patients were required to be stable on SEROQUEL plus lithium or divalproex for at least 12 weeks in order to be randomized. On average, patients were stabilized for 15 weeks. In the randomization phase, patients continued treatment with lithium or divalproex and were randomized to receive either SEROQUEL (administered twice daily totaling 400 to 800 mg per day) or placebo. Approximately 50% of the patients had discontinued from the SEROQUEL group by day 280 and 50% of the placebo group had discontinued by day 117 of double-blind treatment. The primary endpoint in these studies was time to recurrence of a mood event (manic, mixed or depressed episode). A mood event was defined as medication initiation or hospitalization for a mood episode; YMRS score ≥ 20 or MADRS score ≥ 20 at 2 consecutive assessments; or study discontinuation due to a mood event.

In both studies, SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event. The treatment effect was present for both manic and depressed episodes. The effect of SEROQUEL was independent of any specific subgroup (assigned mood stabilizer, sex, age, race, most recent bipolar episode, or rapid cycling course).

## 15 REFERENCES

None

## 16 HOW SUPPLIED/STORAGE AND HANDLING

- 50 mg Tablets (NDC 0310-0280) peach, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 50" 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.

- 150 mg Tablets (NDC 0310-0281) white, film-coated, capsule-shaped, biconvex, intagliated tablet with 'XR 150' 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.

- 200 mg Tablets (NDC 0310-0282) yellow, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 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 "XR 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 "XR 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 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [See USP].

## 17 PATIENT COUNSELING INFORMATION

### 17.1 Information for Patients

[see Medication Guide]

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL XR 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 XR. 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 XR.

### 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 *Warnings and Precautions* (5.2)].

### 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 *Warnings and Precautions* (5.1)].

### Hyperglycemia and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and 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 *Warnings and Precautions* (5.3)].

### Hyperlipidemia
Patients should be advised that elevations in total cholesterol, LDL and triglycerides may occur [see *Warnings and Precautions* (5.4)].

### Weight Gain
Patients should be advised that they may experience weight gain [see *Warnings and Precautions* (5.5)].

### 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 *Warnings and Precautions* (5.6)].

### Orthostatic Hypotension
Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing, which may lead to falls) especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose [see *Warnings and Precautions* (5.8)].

### 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 *Warnings and Precautions* (5.9)].

### Interference with Cognitive and Motor Performance
Patients should be advised of the risk of somnolence or sedation (which may lead to falls), 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 *Warnings and Precautions* (5.16)].

### 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 Specific Populations* (8.1 and 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 [see *Warnings and Precautions* (5.21)].

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions* (5.18)].

## 17.2 Medication Guide

**Medication Guide**

**SEROQUEL XR (SER-oh-kwell)**

**Generic name: quetiapine fumarate**

**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.

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